SYNTHESIS AND PROPERTIES OF AMINO QUINOLIZINIUM SALTS

A THESIS

by

T. L. HOUGH

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SUMMARY

The methods of synthesis and known properties of quinolizinium compounds are reviewed.

A previously reported synthesis of quinolizinium salts has been used to prepare a number of 1- and 2-aminoquinolizinium salts. The method involved the condensation of suitably activated 2-picolinium salts with compounds containing two adjacent oxo groups. Some limitations of the synthetic method are described together with some modifications widening its scope.

The properties of a number of 1- and 2-aminoquinolizinium salts are reported. The bromination of 1-aminoquinolizinium salts occurred in the 2- and 4-positions; 2-aminoquinolizinium salts brominated in the 1-position. The reaction of 1- and 2-aminoquinolizinium salts with nitrous acid gave N- or C-nitrosation, and lead to tricyclic products. When a reactive methyl group was present, inter- or intra-molecular condensation occurred giving in the latter case pyrazolo(3,4-a)quinolizinium salts.

In the last section, a general synthesis of 2-alkylquinolizinium salts is described. The synthetic method involved the alkylation of 2-γ-ethoxybutyryl pyridine. The alkylated products were converted to quinolizinium salts by a previously reported method.

ACKNOWLEDGMENTS

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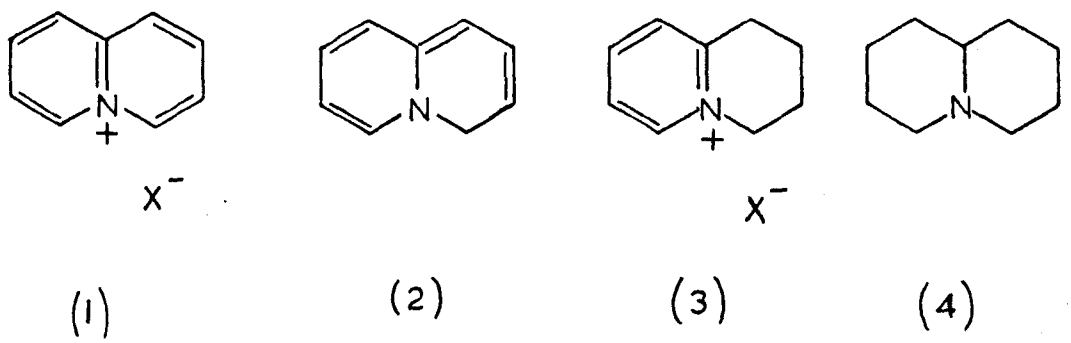
CONTENTS

INTRODUCTION

Nomenclature

Although the terms dehydropyridocolinium ion and dehydroquinolizinium ion have been used to designate the bicyclic naphthalenic ring system with a quaternary bridgehead nitrogen atom (1), the name quinolizinium ion is now in common use and will be used throughout this thesis. The system (2) in which the nitrogen atom is non-quaternary is one (4-H) of several isomers known as quinolizines. The partially reduced system (3) will be referred to as 1,2,3,4-tetrahydroquinolizinium salt and when reference is made to the fully reduced system (4), the name quinolizidine will be used.



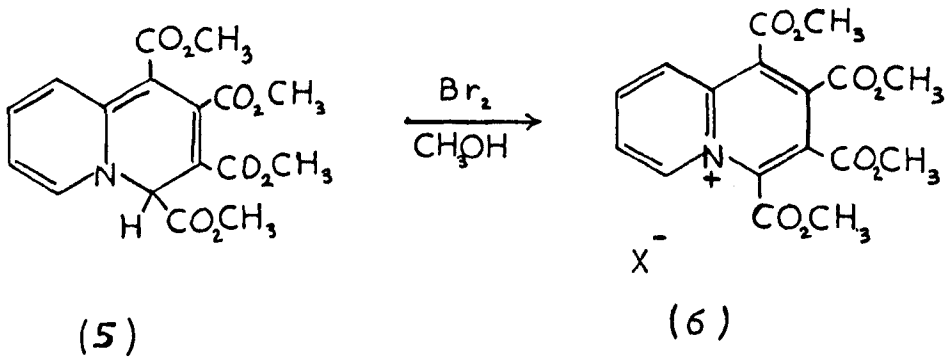
(1) (2) (3) (4)

Historical Introduction

(a) Syntheses of Quinolizinium Compounds

The syntheses of quinolizinium salts have received little attention in the literature by comparison with those of quinolizines and quinolizidines. The first reported synthesis of a quinolizinium compound was by Diels and Alder[1] who prepared the highly substituted

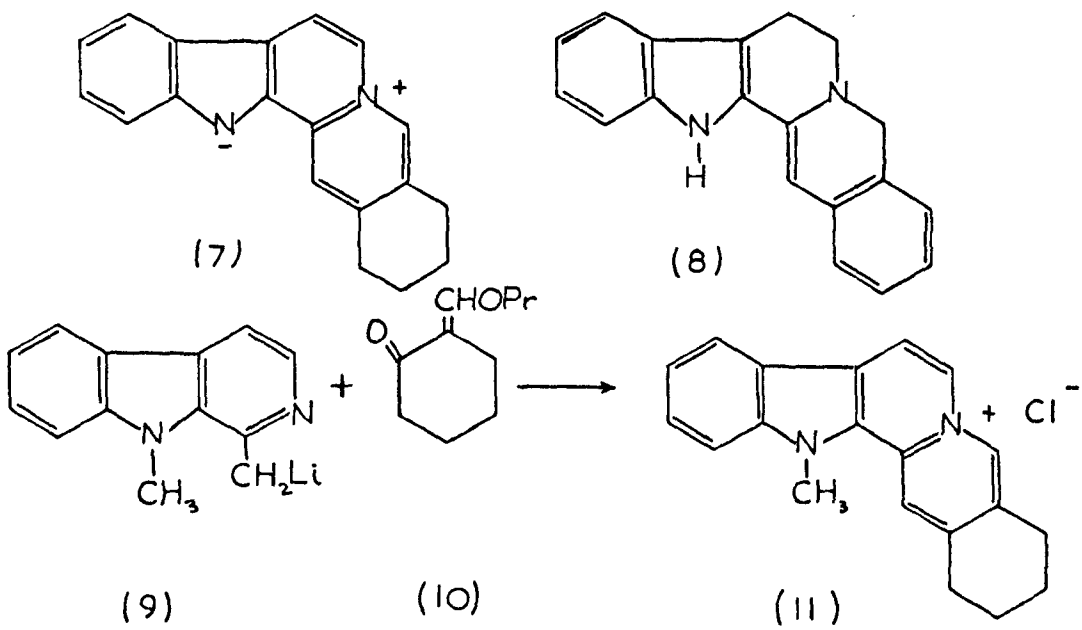
1,2,3,4-tetramethoxycarbonyl compound (6). The starting material for this reaction was 4H-quinolizine-1,2,3,4-tetracarboxylate (5) which was obtained as one of the products of the reaction between pyridine and dimethyl acetylenedicarboxylate. The authors[1] gave the structure of the quinolizine (5) as the 9a-H isomer but Acheson and Taylor[2] and Jackman, Johnson and Tebby[3] have since shown that the correct one is the 4-H compound (5). Oxidation of the quinolizine (5) with bromine in methanol gave the quinolizinium compound, (6). Similar compounds have been obtained using substituted pyridines in the reaction with dimethyl acetylenedicarboxylate.



(5) (6)

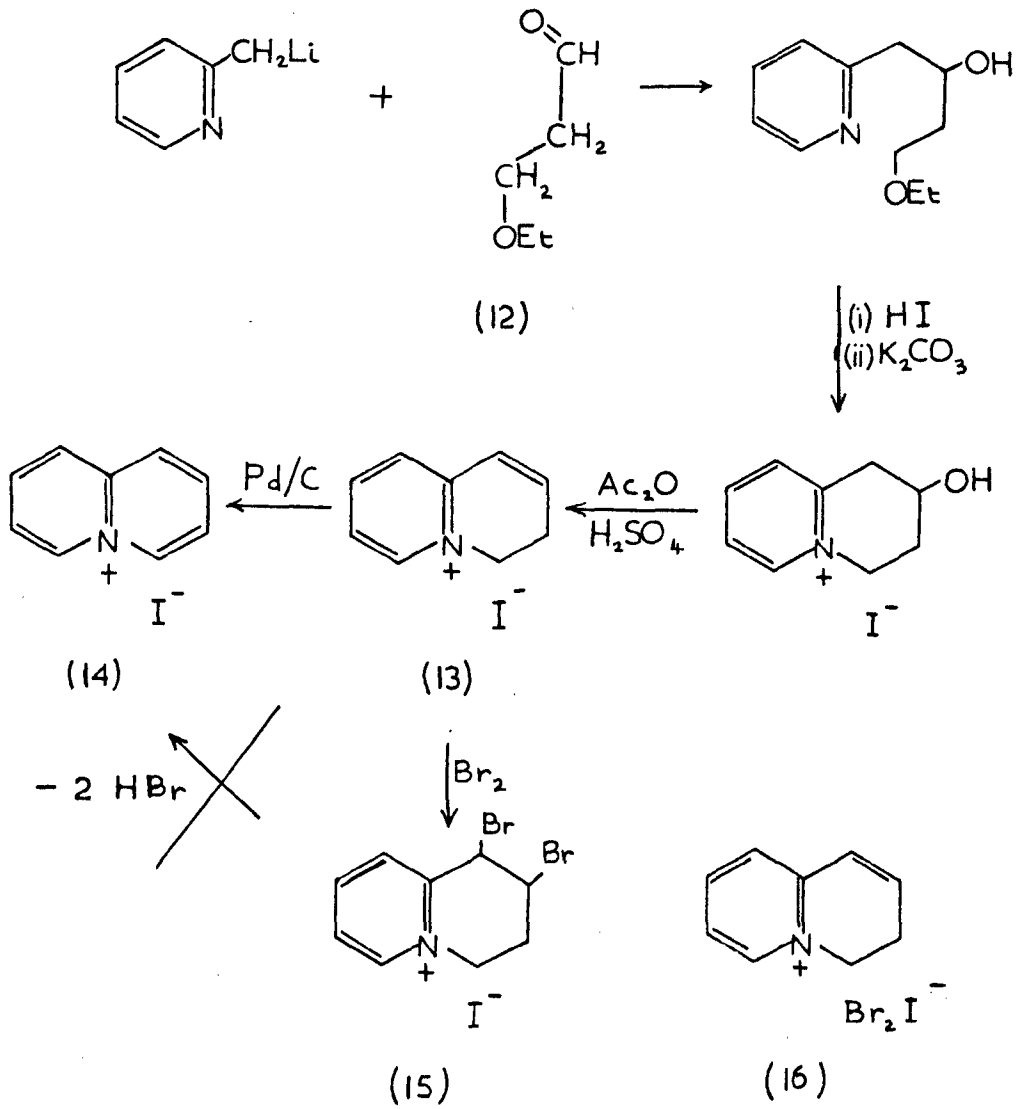
In 1949 Bentley and Stevens[4] and McLamore and Woodward[5] simultaneously established the presence of the quinolizinium system in the alkaloid sempervirine (7). The structure of the alkaloid had previously been formulated as (8)[6] but the synthetic studies of McLamore and Woodward[5] suggest that the bridgehead nitrogen atom has quaternary character. The authors[5] prepared a number of sempervirine metho-salts by a process which involved reaction of 2-isopropoxy-methylene cyclohexanone (10) with the lithium reagent of N-methylharman (9) and

subsequent cyclisation giving 13-methyl-1,2,3,4-tetrahydrobenzoindolo-(2:3-a) quinolizinium chloride (11).



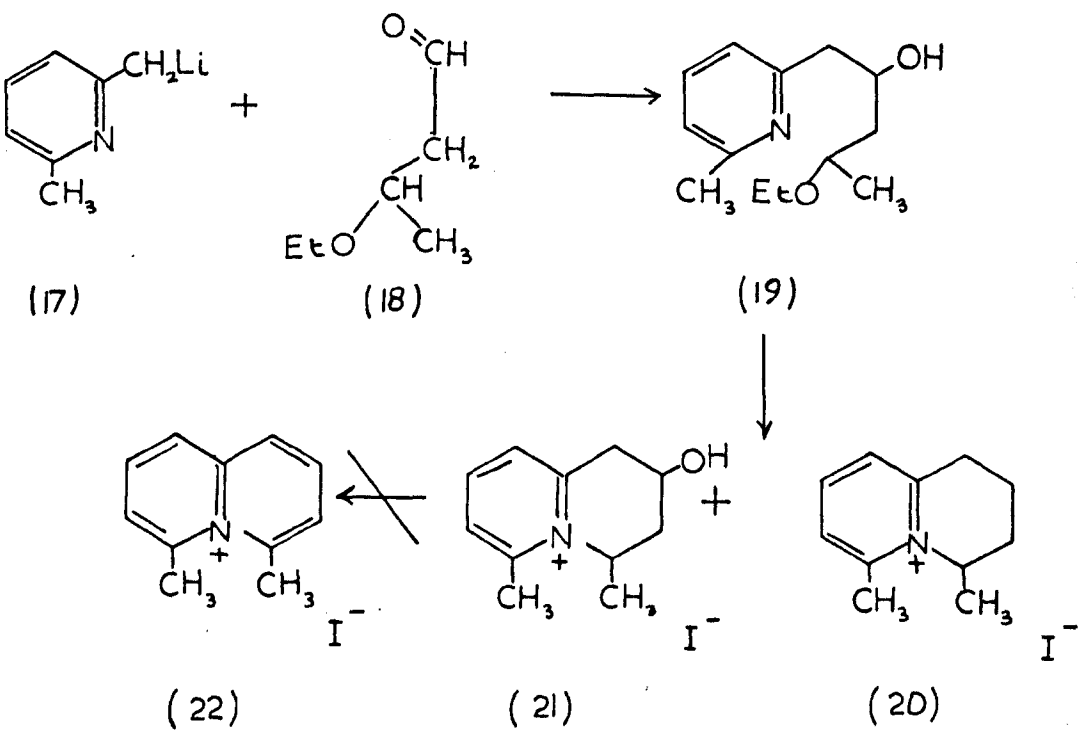
Using a modification of the McLamore and Woodward[5] synthesis, Beaman and Woodward[7] were the first to prepare the unsubstituted quinolizinium system. 2-Picolyllithium was treated with 3-isopropoxy-acrolein and the product cyclised with acid to the quinolizinium ion. The quinolizinium salt, however, could only be isolated with great difficulty and in poor yield. By replacing the 3-isopropoxy-acrolein with the more readily accessible 3-ethoxypropionaldehyde (12), however, Boekelheide and Gall[8] were able to obtain a practical yield of quinolizinium iodide (14). The dehydrogenation of 3,4-dihydroquinolizinium iodide (13) in this reaction scheme, shown below

presented the most difficulty and limited the overall yield based on 3-ethoxypropionaldehyde as starting material to 10%.



Attempts to improve the yield by dehydrobromination of 1,2-dibromo-1,2,3,4-tetrahydroquinolizinium iodide (15) were unsuccessful, probably because, as Richards and Stevens[9] suggest, the intermediate (15) is in fact the mixed salt 3,4-dihydroquinolizinium dibromoiodide (16).

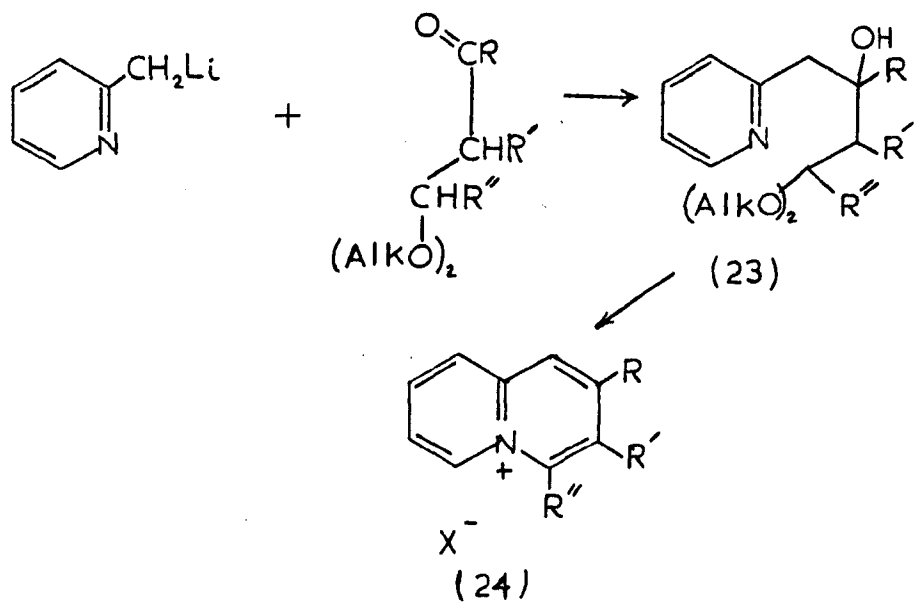
Boekelheide and Ross[10] later extended this method of synthesis to the preparation of 4-methylquinolizinium iodide using the monolithium reagent of 2,6-lutidine in place of 2-picolyllithium. However, when Boekelheide, Fritz, Ross and Kaempfen[11] attempted to prepare 4,6-dimethylquinolizinium iodide (22) by the same method, the intermediate condensation product (19) obtained from the mono-lithium reagent of 2,6-lutidine (17) and 3-ethoxybutyraldehyde (18) gave a mixture of the compounds (20) and (21) on cyclisation.



Attempts to dehydrate or simultaneously dehydrate and dehydrogenate the tetrahydro compound (21) were unsuccessful.

A number of 2-, 2,3- and 2,4- alkyl and aryl substituted quinolizinium salts have been prepared by Richards and Stevens[12] by a

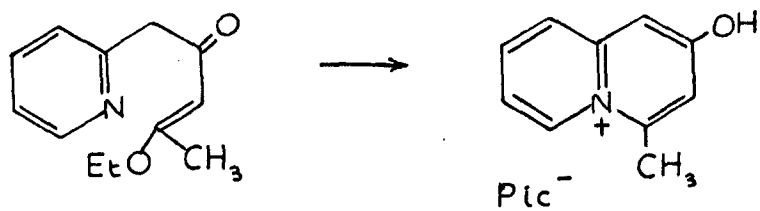
method which is essentially a modification of that described by Doekelheide and his co-workers. The procedure is limited to 2-substituted compounds, but avoids the troublesome dehydrogenation stage. By treating the enol ether or mono-ketal of a β-diketone with 2-picolyllithium, alcohols of the type (23) are obtained. Cyclising these alcohols in acid affords the appropriate substituted quinolizinium salts, (24).



In the same way, Hansen and Amstutz[13] have synthesised 2,4,6-alkyl and aryl quinolizinium salts. This has been accomplished by the reaction of the monolithium reagent of 2,6-lutidine with the suitably protected β-diketone.

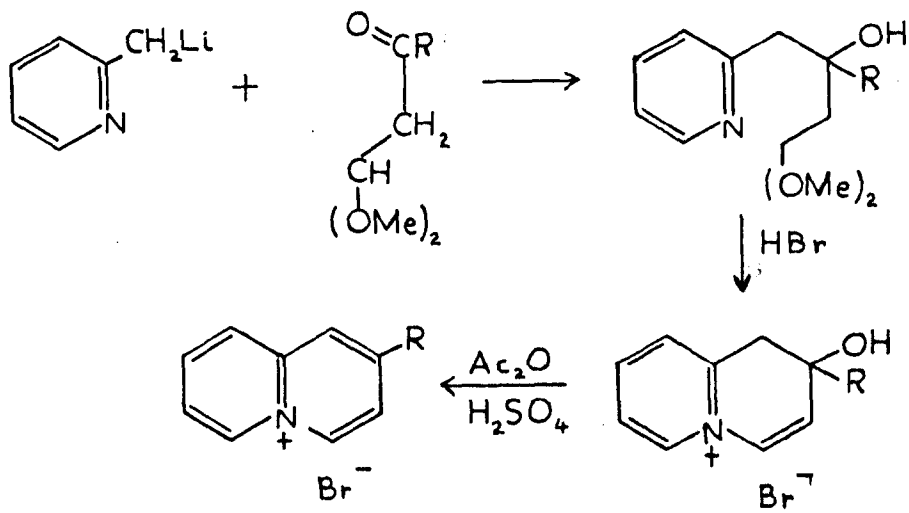
Richards and Stevens[12] also attempted to prepare a quinolizinium salt unsubstituted in the 2-position by reacting 2-picolyllithium with ethyl-β-ethoxycrotonate giving compound (25). With picric acid an

unstable picrate was formed and has been formulated as 2-hydroxy-4--methylquinolizinium picrate (26).



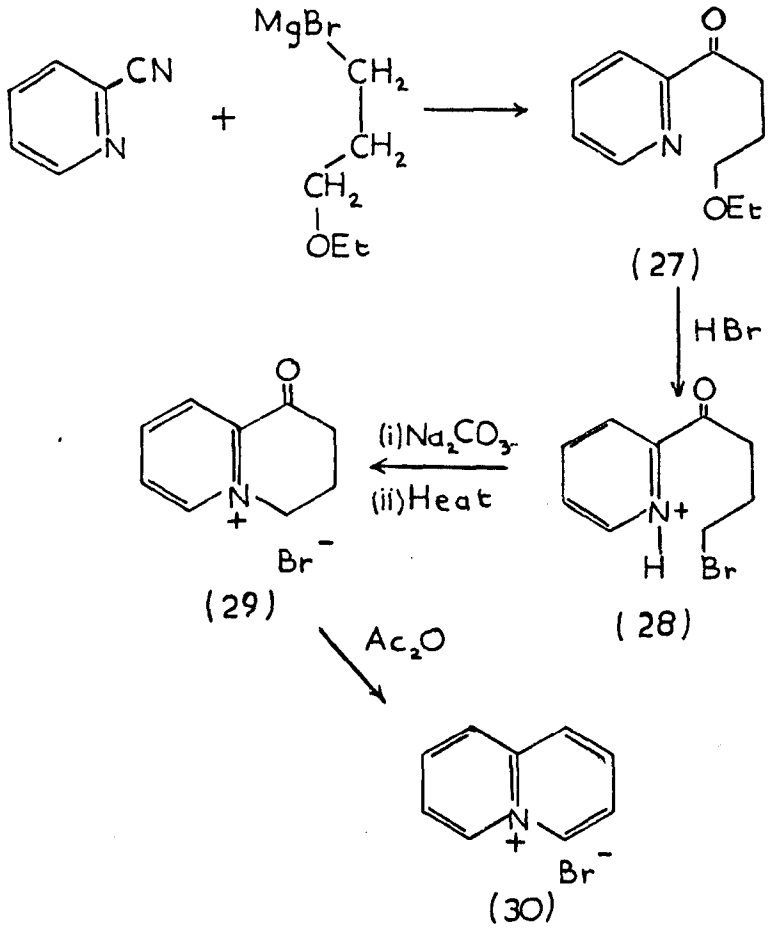
(25) (26)

Another modification is reported by Nesmeyanov and Rybinskaia[14] who describe the synthesis of 2-alkyl and 2-arylquinolizinium salts by the treatment of α-acylacetals with 2-picolyllithium followed by cyclisation in boiling hydrobromic acid and dehydration with acetic anhydride containing a trace of sulphuric acid.



A synthesis by Glover and Jones[15] was the first to produce the unsubstituted quinolizinium system in appreciable quantities. By treating 2-cyanopyridine with the Grignard reagent from 3-ethoxypropyl bromide they

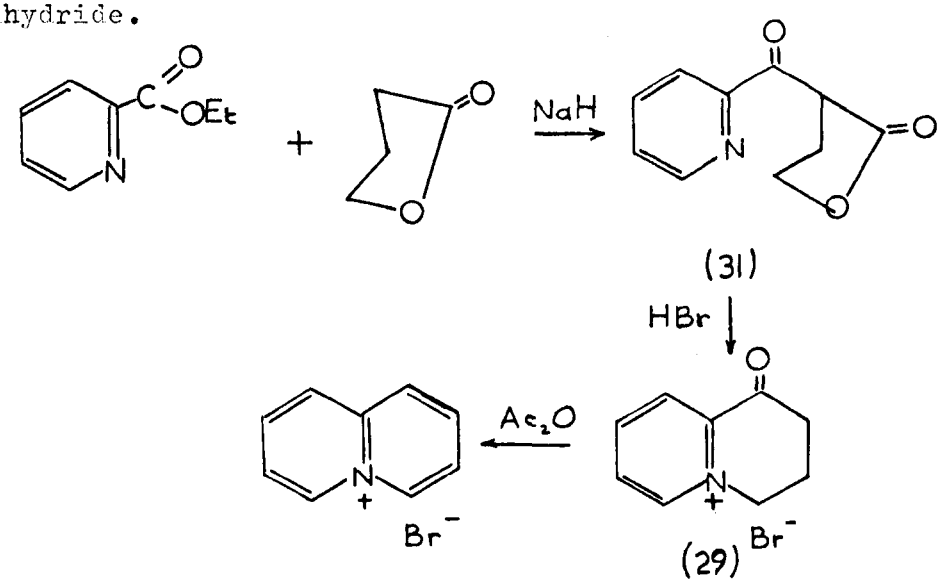
obtained 2-(4'-cthoxybutyryl)pyridine (27) which was cyclised to give 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (29). The cyclic ketone (29) was aromatised to quinolizinium bromide (30) by refluxing in acetic anhydride. An overall yield of 48% was recorded based on the 2-cyano-pyridine.



Using suitable starting materials, the authors[15,16] have extended the method to include the synthesis of 2-, 3- and 4-alkyl and aryl substituted quinolizinium salts.

A modification of the Glover and Jones[15] synthesis is reported by Miyadera and Iwai[17] who condensed 2-ethylpicolinate with γ-butyrolactone

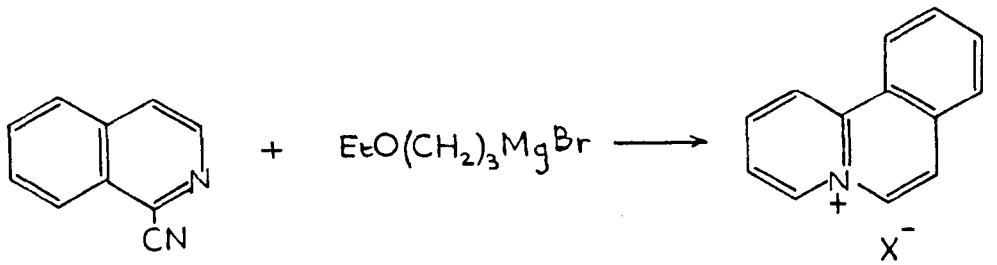
giving the keto-lactone (31). Treatment with hydrobromic acid gives the cyclic ketone (29) which is aromatised in refluxing acetic anhydride.



The synthesis is a general one and has been extended to the preparation of 1-, 2-, 3- and 4-methyl quinolizinium salts in good yield.

Syntheses of the cyclic ketone (29) are also reported by Prasad and Swan[18] and Ilderfield, Lagowski, McCurdy and Wythe[19] although in lower yields that either of the preparations described above. The synthesis of 1-oxo-1,2,3,4-tetrahydro-7-ethylquinolizinium bromide is reported by Kaneko.[20]

By suitably adapting their quinolizinium synthesis, Glover and Jones[16] prepared the benzo-(a) (31), benzo-(b) (32) and benzo-(c) (33) quinolizinium salts. All three isomers were made from the appropriate cyanoquinoline or cyanoisoquinoline and the Grignard reagent from 3-ethoxypropyl bromide.



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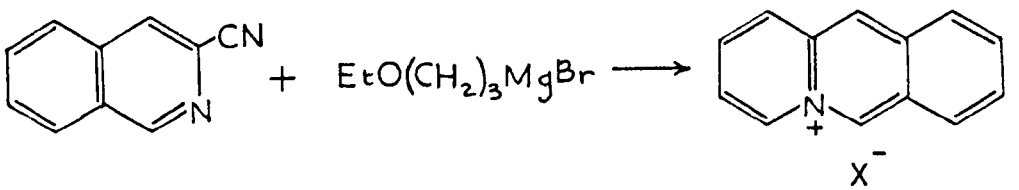

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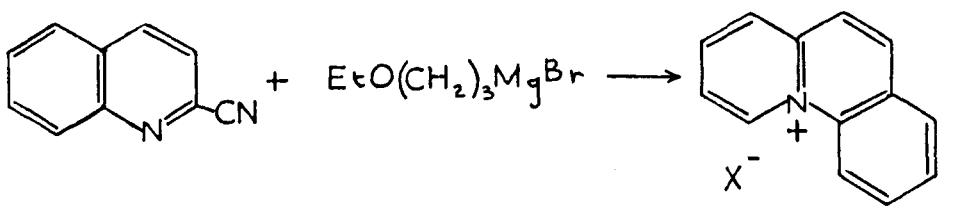
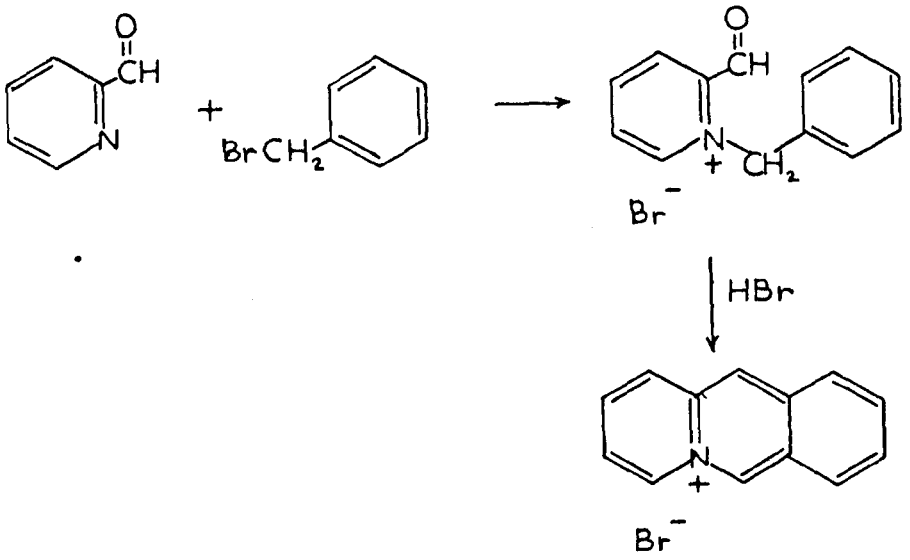


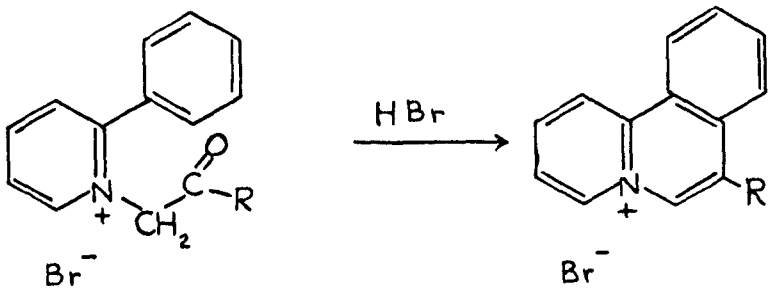
(33)

Most of the work on the synthesis of benzo-quinolizinium salts, however, has been done by Bradsher and his co-workers. Two methods have been employed in these syntheses: aromatic cyclodehydration reactions and photochemical reactions. Bradsher and Beavers[21] thus reported the first synthesis of benzo (b) quinolizinium bromide (34) by cyclodehydrating the quaternary salt from pyridine-2-aldehyde and benzyl bromide in hydrobromic acid. Using 2- or 3-substituted benzyl bromide gave the corresponding substituted benzo(b)quinolizinium bromide.



(34)

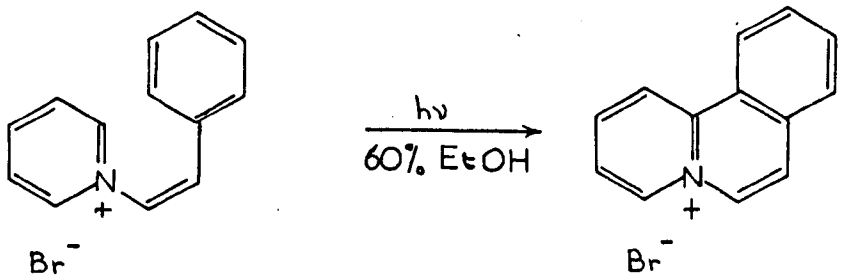
In the same way, Bradsher and Jones[22] prepared a number of substituted benzo(a)quinolizinium salts. In this case, 2-phenyl pyridine was quaternised with iodoacetone and with phenacyl bromide and the pyridinium compounds cyclised to 7-methyl (35, R = CH_3) and 7-phenyl (35, R = Ph) benzo(a)quinolizinium bromides, respectively.



(35)

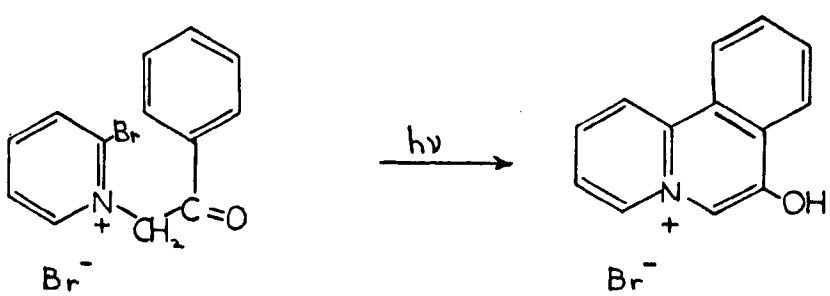
Bradsher and Beavers[23] have demonstrated how the method of aromatic cyclodehydration can also be applied to the synthesis of linear and angular tetracyclic quinolizinium compounds. The photochemical reactions have been used to synthesise substituted and unsubstituted benzo (a) and

benzo(c)quinolizinium salts. Benzo(a)quinolizinium bromide (36) was obtained[24] in 60% yield by the irradiation of 1-styrylpyridinium bromide.



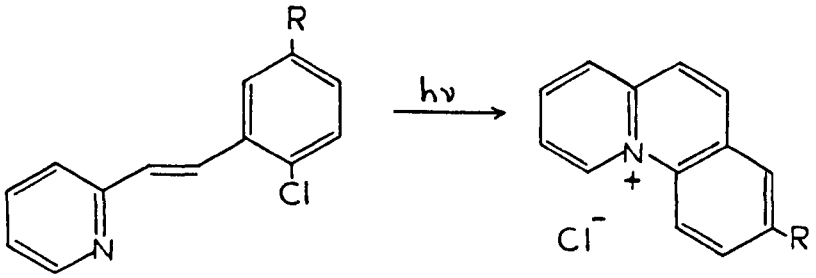
(36)

The quaternary salt from phenacyl bromide and 2-bromopyridine similarly underwent cyclisation but with simultaneous enolisation to 7-hydroxy-benzo(a)quinolizinium bromide (37).

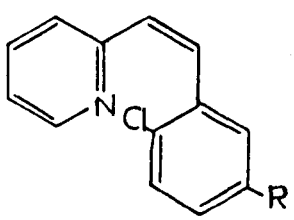


(37)

Bradsher and Fozard[25] synthesised 9-nitrobenzo(c)quinolizinium chloride (39, R = NO_2) by the irradiation of trans-2'-chloro-4'-nitro-2-stilbazole (38, R = NO_2). Presumably, cyclisation is preceded by isomerism to the cis compound (40, R = NO_2), and is aided by the nitro-group, because, without the activating group, trans-2'-chloro-2-stilbazole (38, R = H) isomerised to the corresponding cis compound (40, R = H) which could be cyclised only on heating.

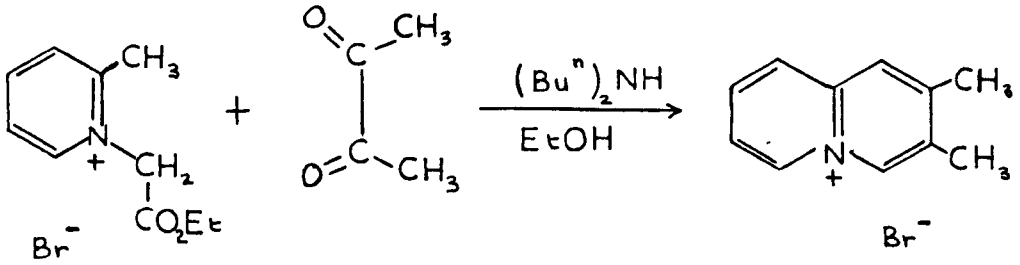


(38) (39)



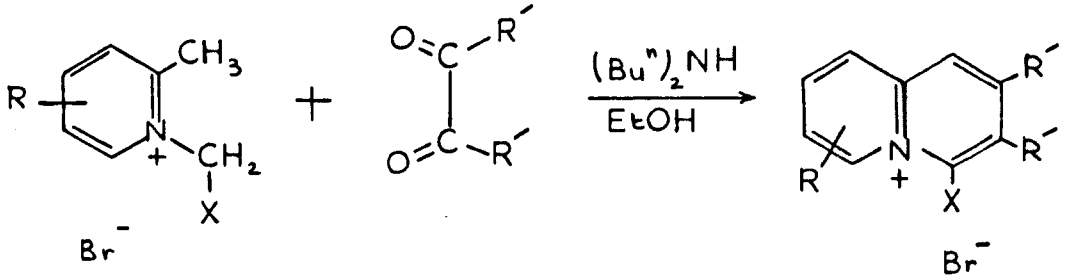
(40)

A number of di-substituted quinolizinium compounds have been prepared by Westphal, Jahn and Heffe[26] in reactions which involve the condensation of suitably activated 2-picolinium salts with compounds containing two adjacent oxo-groups. Thus, by refluxing an ethanolic solution of the quaternary salt (41), obtained from ethyl bromoacetate and 2-picoline, with diacetyl and di-n-butylamine as the basic catalyst, 2,3-dimethyl quinolizinium bromide (42) is obtained.



(41) (42)

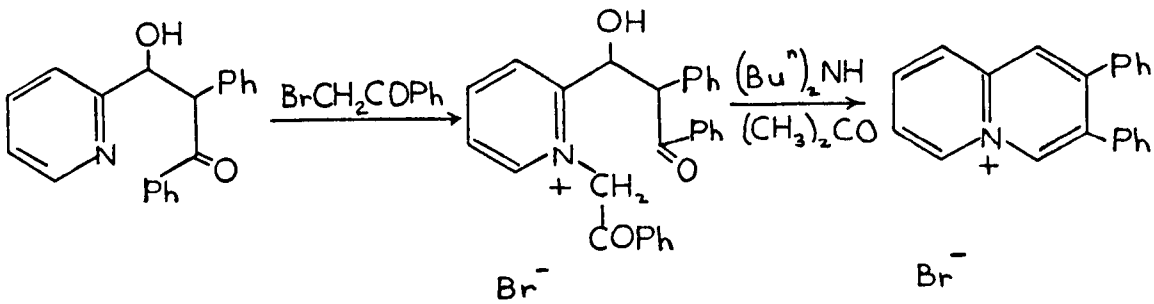
The quaternary salt of 2-ethylpyridine has been cyclised in the same way to give 1,2,3-trimethylquinolizinium bromide and the reaction has been extended to include the synthesis of di-substituted benzoquinolizinium salts by employing the quaternary salts of 1-methylisoquinoline and quinaldine. The reaction was also successful when furil was used in place of diacetyl, giving 2,3-di-α-furyl compounds. The same method has been used extensively in a patent[27] which lists the preparation of a number of di-substituted quinolizinium salts with various substituents in the 6-, 7- and 8-positions and indicates that cyclisation also occurs when the methylene in the pyridinium salt is activated by -CN, -COPh or $-CONH_2$ but usually with retention of the functional group in the 4-position of the quinolizinium salt.



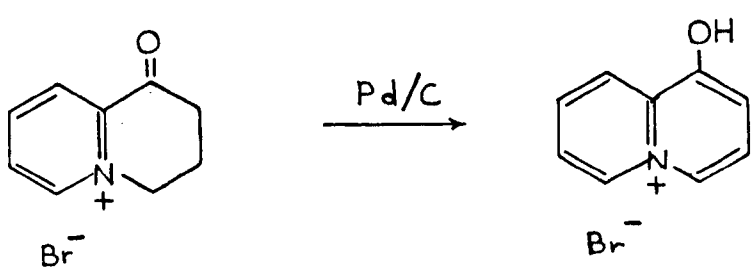
X = -CN, -COPh, $-CONH_2$

k' = Me, Ph, anisyl, α-furil, α-pyridyl

A modification of the method is described by Westphal and Feix[28] who prepared 2,3-diphenyl quinolizinium bromide by first reacting 2-pyridinealdehyde with phenyl benzyl ketone. The product was quaternised with phenacyl bromide and the resulting pyridinium salt cyclised by refluxing with a solution of di-n-butylamine in acetone.



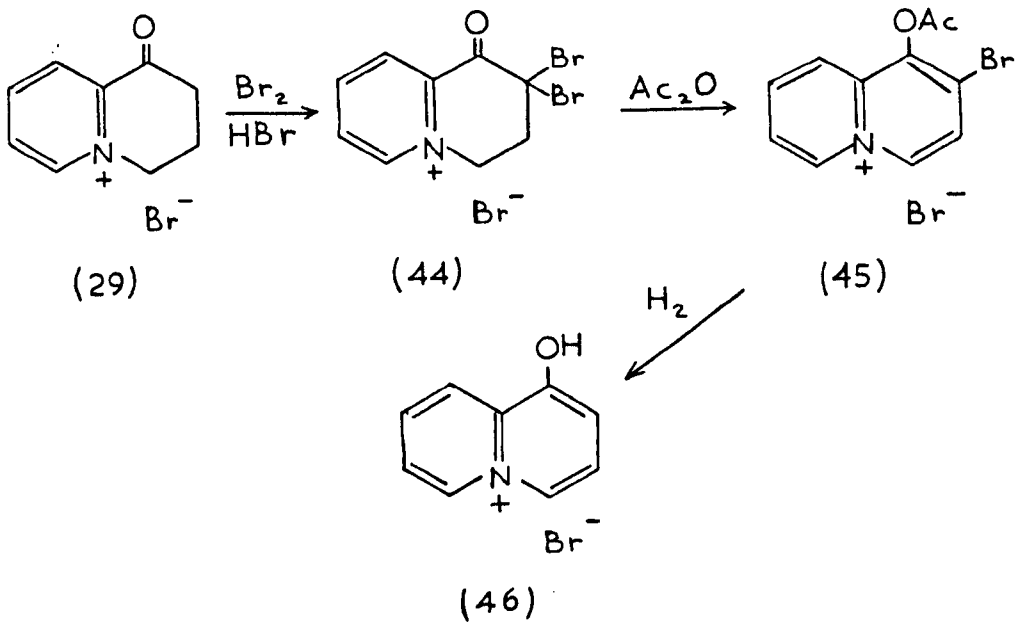
Most of the preparative studies on quinolizinium salts containing reactive groups have been concerned with the synthesis of hydroxy quinolizinium compounds. 1-Hydroxy quinolizinium salt (43) was first prepared by Glover and Jones[29] by dehydrogenation of 1-oxo-1,2,3,4--tetrahydroquinolizinium bromide (29) with palladium charcoal.



(29) (43)

The yield from this reaction was poor and only the picrate was isolated. However, from the same cyclic ketone (29), Fozard and Jones[30] obtained the bromide in good yield. The addition of two moles of bromine to the ketone (29) gave 1-oxo-2,2-dibromo-1,2,3,4-tetrahydroquinolizinium bromide (44)

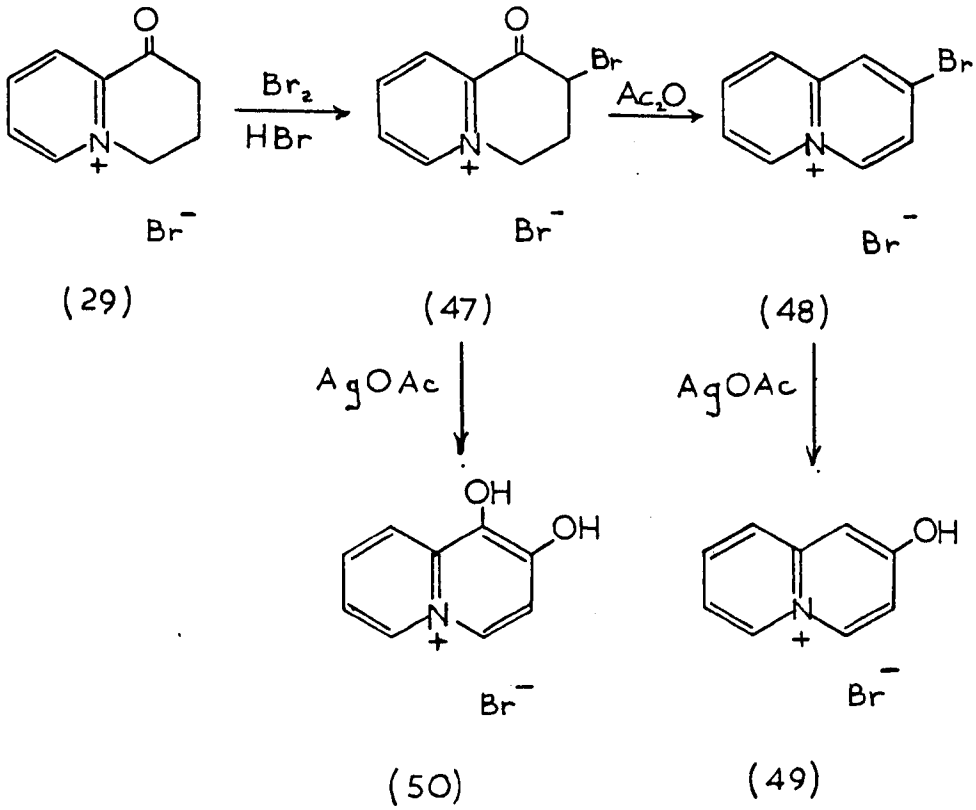
in 90% yield and this was aromatised in boiling acetic anhydride to 1-acetoxy-2-bromoquinolizinium bromide (45). Catalytic reduction of the bromo-acetoxy compound (45) gave 1-hydroxyquinolizinium bromide (46).



(29) (44) (45)

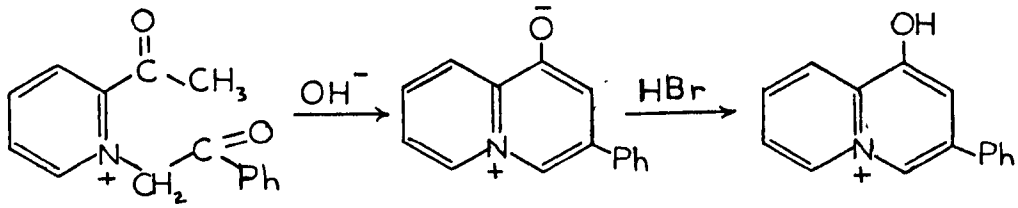
(46)

Fozard and Jones[31] also report the synthesis of 2-hydroxyquinolizinium bromide (49). Again the authors use the cyclic ketone (29) as their starting material. Mono-bromination of the ketone gave 1-oxo-2-bromo--1,2,3,4-tetrahydroquinolizinium bromide (47) which aromatised in boiling acetic anhydride to 2-bromoquinolizinium bromide (48). Nucleophilic replacement of -Br by -OH was achieved in 90% yield by reaction with silver acetate.



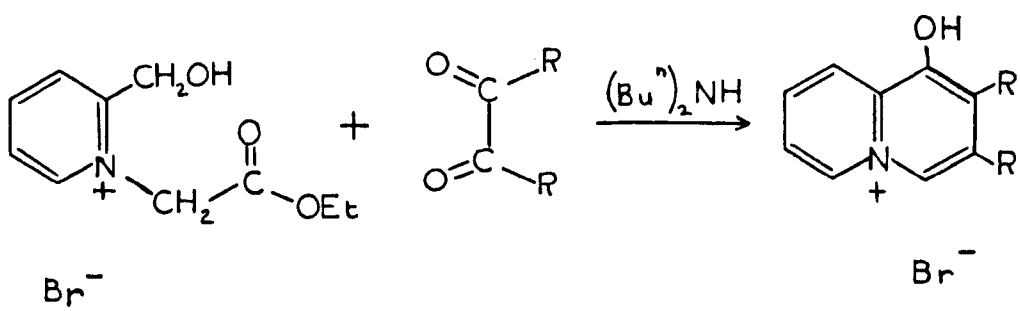
The same authors[31] report the synthesis of 1,2-dihydroxyquinolizinium bromide (50) by the action of silver acetate on the bromo-ketone (47) .

The synthesis of 1-hydroxy-3-phenylquinolizinium bromide (53) is discussed by Kröhnke[32] in a review on pyridinium salts. The quaternary salt (51) from 2-acetylpyridine and phenacyl bromide cyclises to the zwitterion (52) of the 1-hydroxy compound on treatment with base. The zwitterion is not isolated but with hydrobromic acid gives the 1-hydroxy-3-phenyl compound (53) in 80% yield.

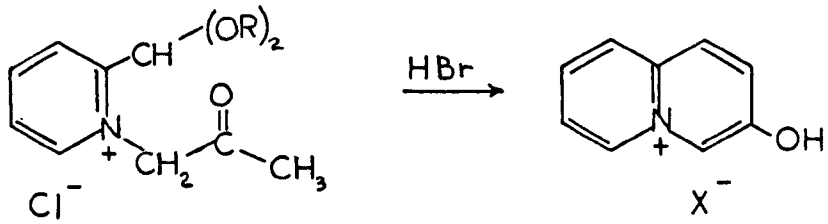


(51) (52) (53)

Using the same general method, Krőhnke, Schnegelberger and Weiss[33] report the synthesis of 2-alkyl-3-aryl substituted 1-hydroxy-quinolizinium salts. The authors[36] also give the preparation of 2,3-dialkyl and diaryl substituted 1-hydroxy-quinolizinium salts by the intermolecular cyclisation of the quaternary salt from ethyl bromoacetate and 2-hydroxymethylpyridine with the appropriate α-diketone.



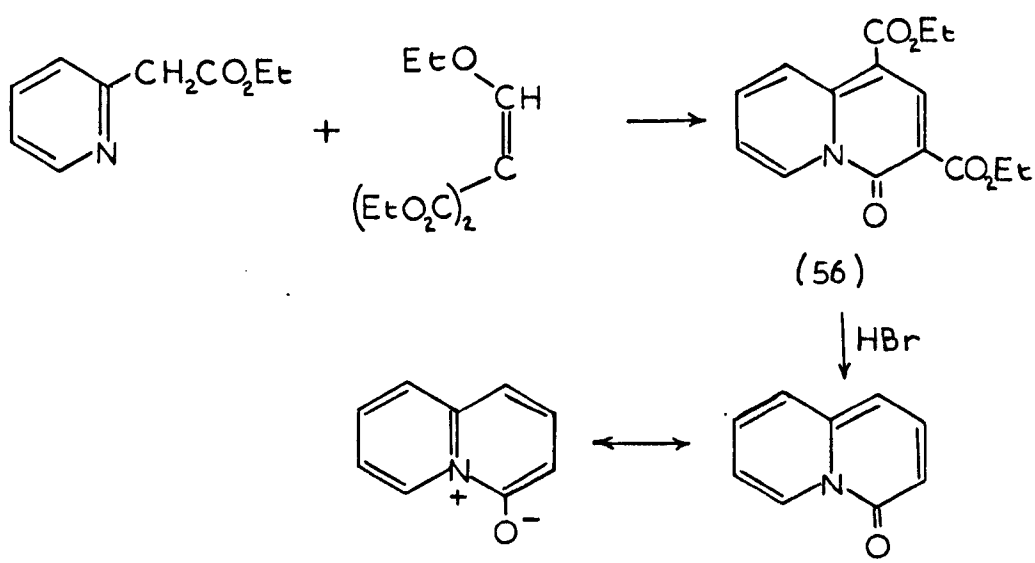
The 3-hydroxyquinolizinium salt (55) was first prepared by Schraufstätter.[34] The synthesis involved the preparation of the quaternary salt (54, R = Et) from 2-pyridineacetal and chloroacetone with subsequent cyclodehydration in hydrobromic acid.



(54) (55)

Although no yields were given, Duke, Fozard and Jones[35] performed the same synthesis on the quaternary salt (54, R=CH_2) of 2-(2-dioxolanyl) pyridine and obtained 3-hydroxyquinolizinium bromide in 96% yield.

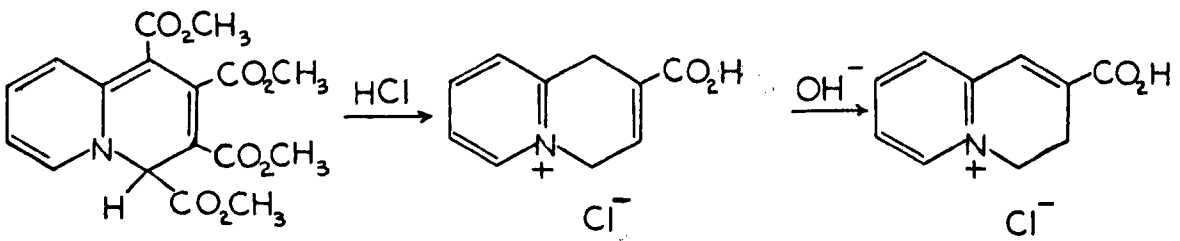
The 4-hydroxyquinolizinium ion (58) which exists in the more stable form as 4-quinolizone (57) was first prepared by Boekelheide and Lodge[36] by the condensation of ethyl pyridyl acetate with diethyl ethoxymethylene malonate to give 1,3-dicarbethoxy-4-quinolizone (56). Decarboxylation in hydrobromic acid gave 4-quinolizone.



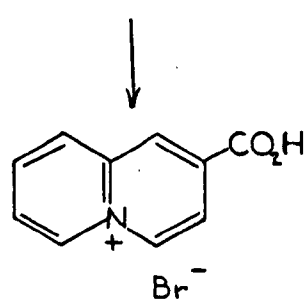
(56)

(58) (57)

By comparison with hydroxyquinolizinium salts the synthesis of carboxyquinolizinium salts has received little attention in the literature. Acheson, Gagan and Taylor[37] report a method of preparing 2-carboxy-1,4-dihydroquinolizinium chloride (59) by the acid hydrolysis of tetramethyl-4H-quinolizine-1,2,3,4-tetracarboxylate. Under basic conditions the 1,4-dihydro compound isomerises to the 3,4-dihydro analogue (60), and aromatises to 2-carboxyquinolizinium bromide (61) with N-bromosuccinimide using aqueous dioxan as solvent.

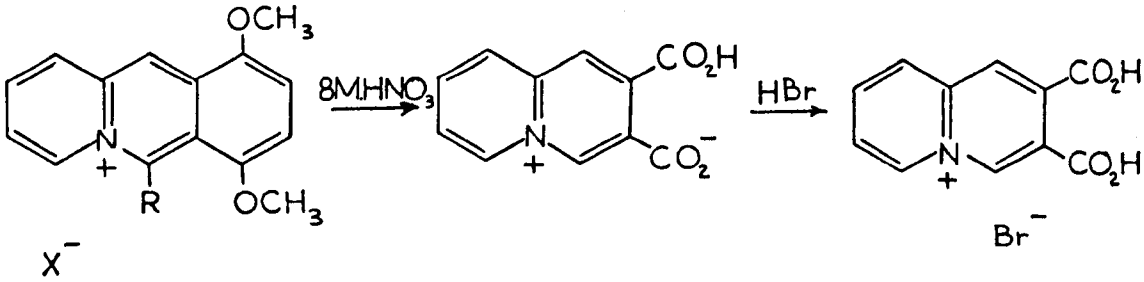


(59) (60)



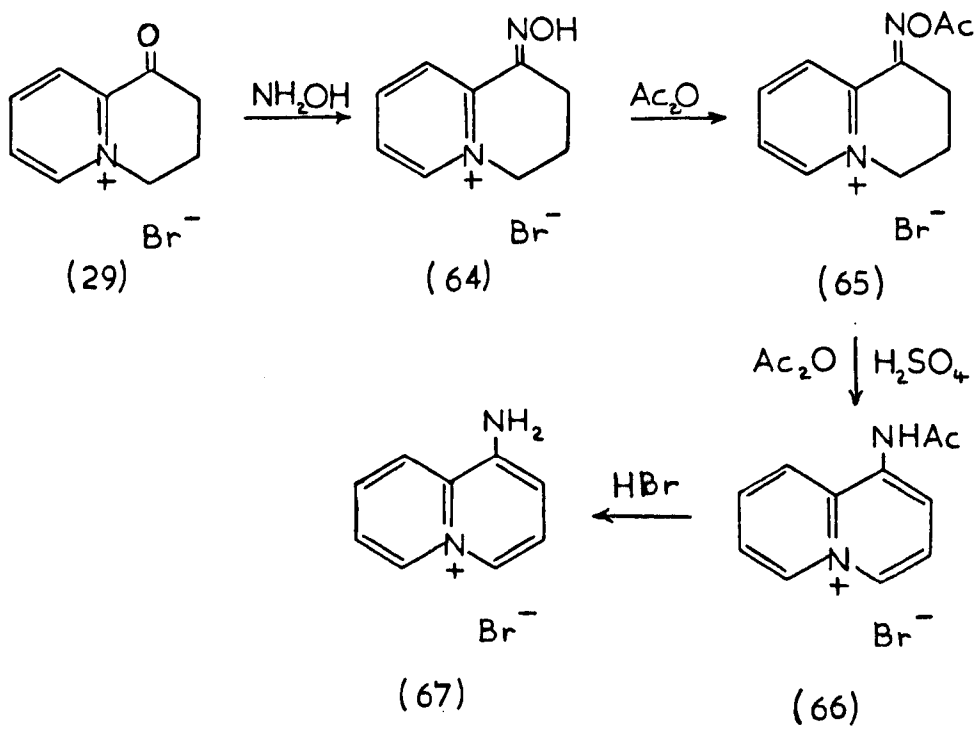
(61)

Bradsher and Barker[38] have studied the oxidation of benzo(b)quinolizinium salts under various conditions. With suitable activating groups (e.g. R = CCH_3) in ring C, the tricyclic compound is oxidised by 8M nitric acid to the 3-carboxylate (62) of 2,3-dicarboxyquinolizinium bromide.



(62) (63)

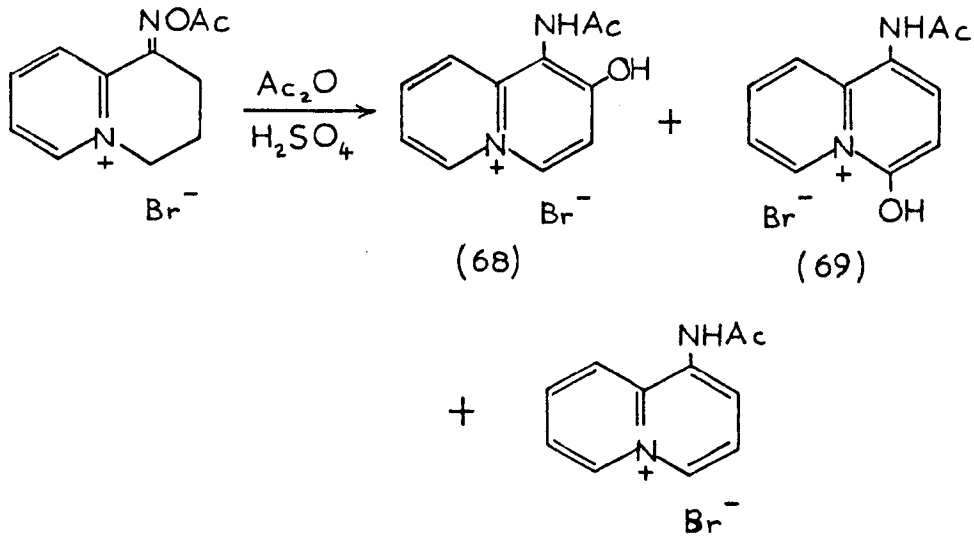
The only reported synthesis to date of an amino-quinolizinium salt is by Collicut and Jones[39] from 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (29). Refluxing the oxime (64) of this ketone (29) in acetic anhydride containing a trace of sulphuric acid initially gave the O-acetyl derivative (65) which underwent Wolff aromatisation to 1-acetamidoquinolizinium bromide (66). Acid hydrolysis of this amide (66) gave 1-aminoquinolizinium bromide (67) as the hydrobromide.



(29) (64) (65)

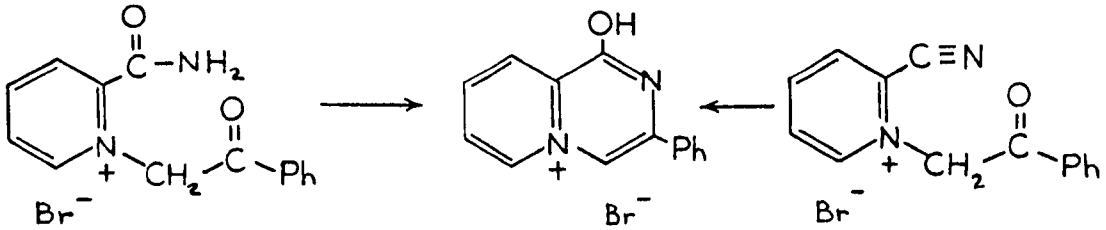
(67) (66)

In the original synthesis the only compound isolated in Wolff aromatisation was the acetamido compound (66). However, when this reaction was later repeated[40] a mixture of 1-acetamido-2-hydroxy (68) and 1-acetamido-4-hydroxy (69) quinolizinium bromide was obtained in addition to the acetamido compound (66).



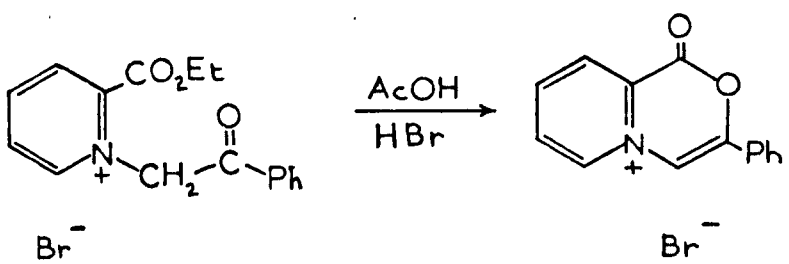
The synthesis of a number of 1- and 2-aminoquinolizinium salts is described later in this work.

Other quinolizinium salts of interest include the substituted 2-oxo and 2-aza analogues prepared by Kröhnke, Schnegelberger and Weis.[33] 1-Hydroxy-3-phenyl-2-azaquinolizinium bromide (68) was formed spontaneously by the cyclodehydration of the quaternary salts (67) and (69) obtained from 2-aminopyridine and 2-cyanopyridine, respectively, and phenacyl bromide.



(67) (68) (69)

A number of 3-substituted 2-oxo analogues were prepared in a similar way. Thus, ethyl picolinate was quaternised with phenacyl bromide and the resulting quaternary salt (70) cyclised by a mixture of acetic acid and hydrobromic acid to 1-oxo-3-phenyl-2-oxoquinolizinium bromide (71).



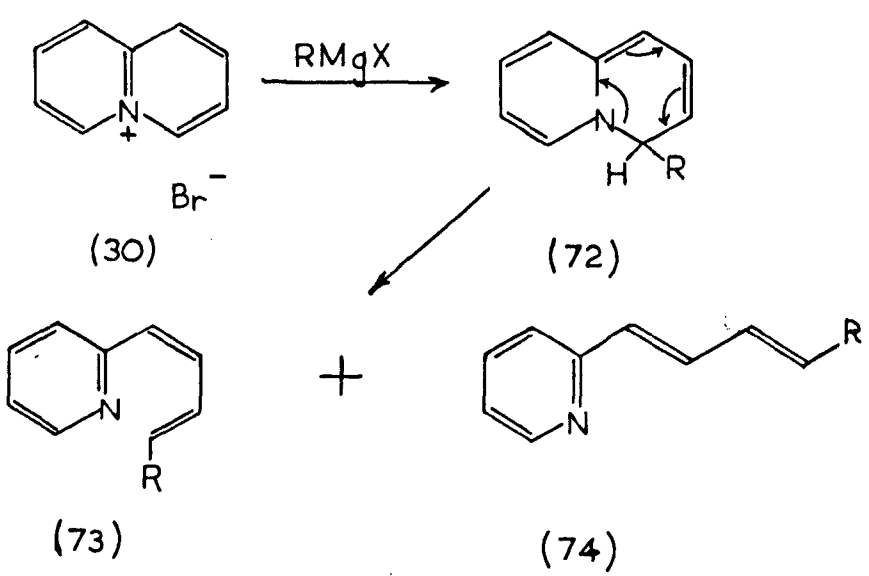
(70) (71)

Using the same general method, Bradsher and Telang[41] have synthesised 3-methyl-2-azaquinolizinium-N-oxide.

Properties of Quinolizinium Salts.

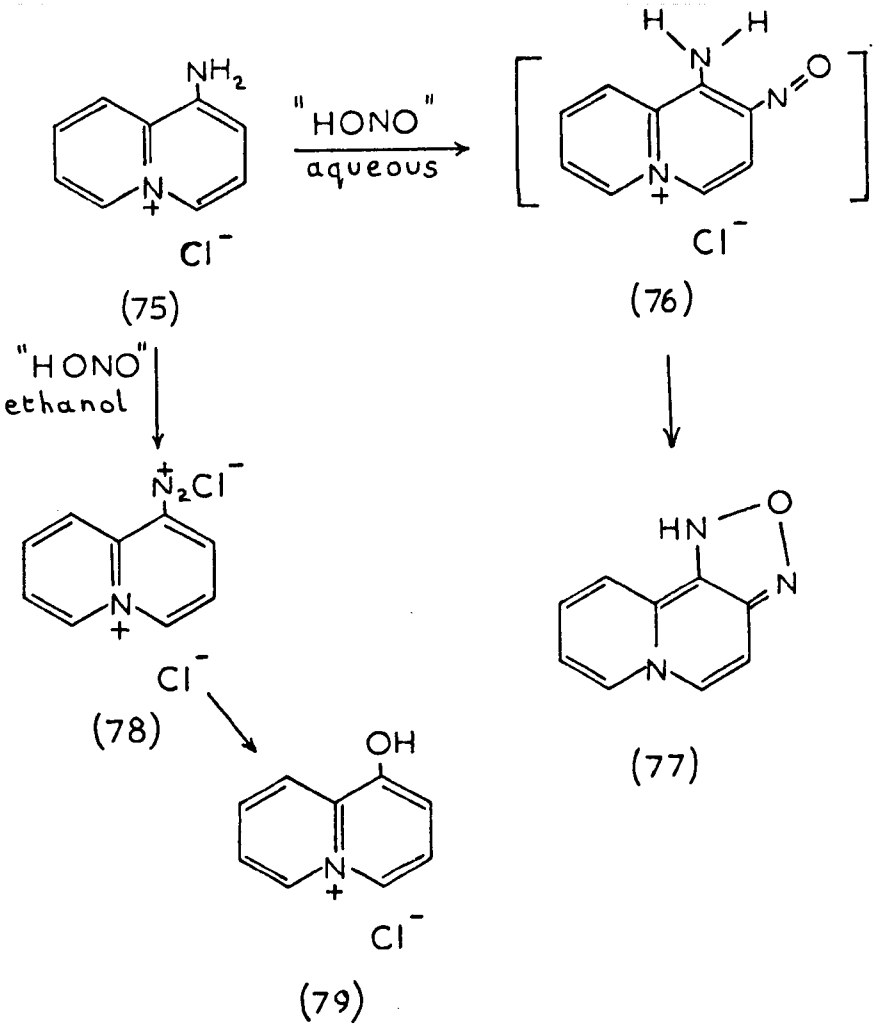
The ultraviolet absorption spectrum of the quinolizinium system is very similar in character to that of quinoline and isoquinoline and confirms its highly aromatic nature. The fact that it forms a crystalline picrate and perchlorate and

exists in a cationic form with chloride, bromide or iodide as the anion is indicative of its ionic character. As an aromatic system carrying a delocalised positive charge we would therefore expect the quinolizinium ion to be deficient of π-electrons and very susceptible to nucleophilic attack. The calculations of Acheson and Goodall[42] indicate that the π-electron densities in the quinolizinium system are least in the 2 and 4 positions and this, together with analogies drawn from pyridine and quinoline chemistry, implies that the nucleophilic attack should predominate in these positions. This has been confirmed to some extent by the work of Miyadera[43] on the reaction of Grignard reagents with quinolizinium bromide (30). The nucleophilic species attacks the 4-position of the cation but with subsequent ring opening giving, as the main product, 1-cis-3-trans-pyridyl butadiene (73). The 1-trans-3-trans-isomer (74) is produced in small yield. The intermediate in this reaction is thought to be the 4-H quinolizine (72) which rearranges to the more stable pyridylbutadienes.

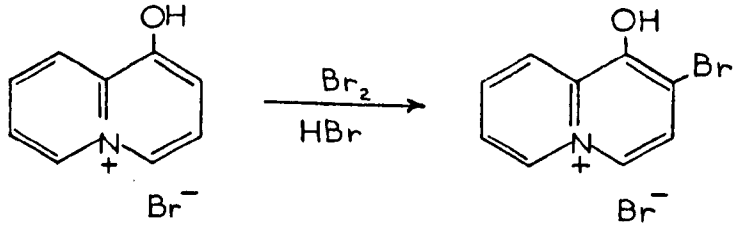


Similar reactions on 1-, 2-, 3- and 4-methyl quinolizinium bromides occurred with ring opening, in most cases the nucleophile attacking the unsubstituted ring. Identical results were obtained by Miyadera and Nishida[44] and Iwai, Ohi, Miyadera and Kawano[45] from reactions between substituted and unsubstituted quinolizinium salts and lithium aluminium hydride.

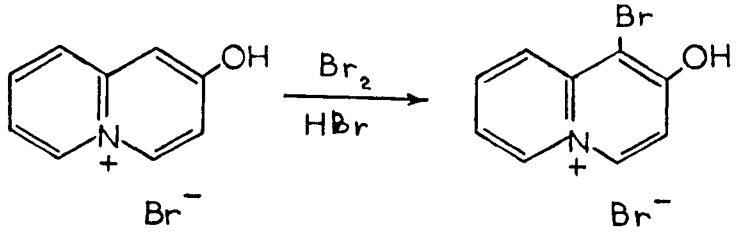
Because of the quaternary nature of the quinolizinium ion, electrophilic substitution should take place much less readily than in pyridine or quinoline. It is noteworthy, however, that the introduction of a single powerful electron-donating group activates the quinolizinium system sufficiently to allow substitution to occur under apparently electrophilic conditions. The work of Collicut and Jones[39] on 1-aminoquinolizinium chloride (75) provides indirect evidence of electrophilic attack at position 2. Attempted diazotisation in aqueous solution gave an insoluble compound of composition $C_9H_7N_3O$. This has been formulated as a furazan (77). The mechanism of this reaction is presumed to involve C-nitrosation of the amine in the 2 position giving 1-amino-2-nitrosoquinolizinium chloride (76) which cyclises to the furazan. In ethanolic solution the amino compound diazotises in the expected way giving 1-hydroxyquinolizinium chloride (79) via the diazonium salt, (78).



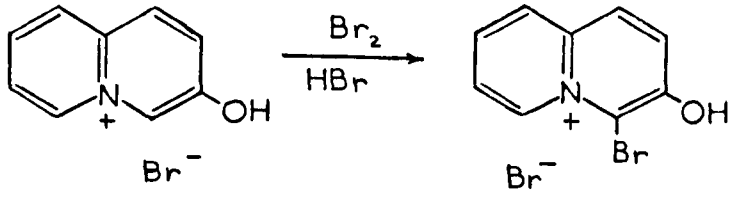
More direct evidence has been accumulated by Bozard and Jones[30,31,35] who have shown that hydroxyquinolizinium salts readily undergo electrophilic substitution. The bromination of 1-, 2- and 3-hydroxyquinolizinium bromides (46,49 and 80) in hydrobromic acid gave, respectively, 1-hydroxy-4-bromo, 1-bromo-2-hydroxy and 3-hydroxy-4-bromo quinolizinium bromides (81,82 and 83). The yields were of the order of 90% and in the latter two cases no isomeric hydroxy compounds were obtained indicating a 'naphthalene' or 'isoquinoline' pattern of di-substitution.



(46) (81)

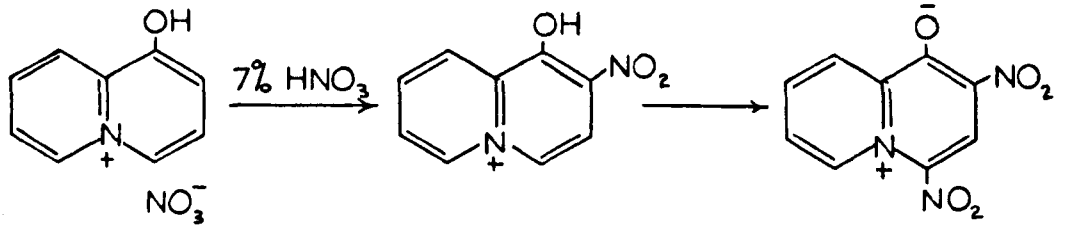


(49) (82)



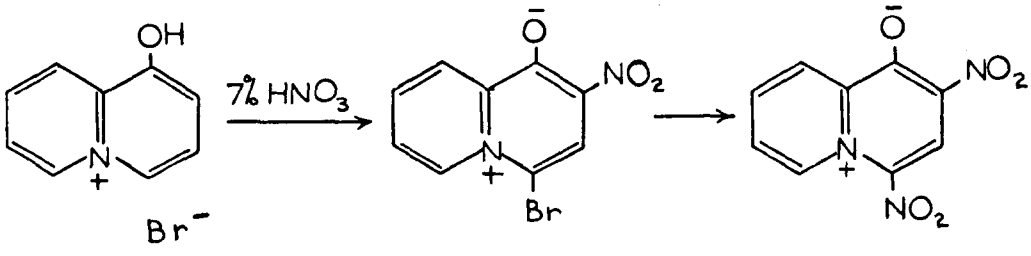
(80) (83)

The nitration of these hydroxy compounds has also been studied.[30,31,35] 1-Hydroxyquinolizinium nitrate (84) when refluxed in 7% nitric acid initially gives the zwitterion (85) of the 1-hydroxy-2-nitroquinolizinium salt. Prolonged boiling gives the 1-hydroxy-2,4-dinitro zwitterion (86).



(84) (85) (86)

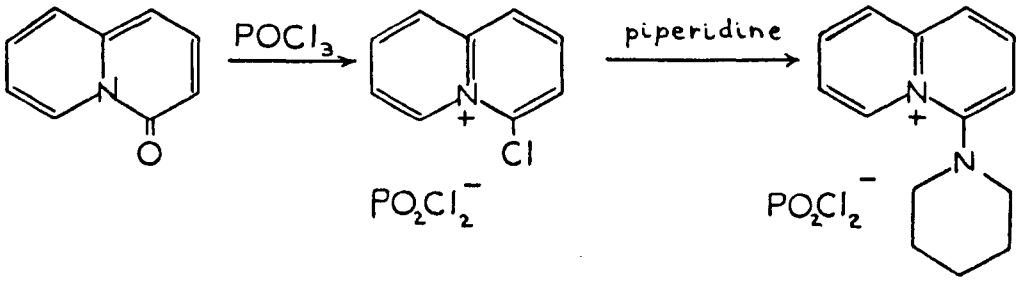
The nitration of 1-hydroxyquinolizinium bromide (46) has been shown to take place concurrently with bromination. Substitution of NO_2 and Br occurs in positions 2 and 4, respectively, giving the zwitterion (87). Further reaction occurs with replacement of Br by NO_2 giving the dinitro zwitterion (86).



(46) (87) (86)

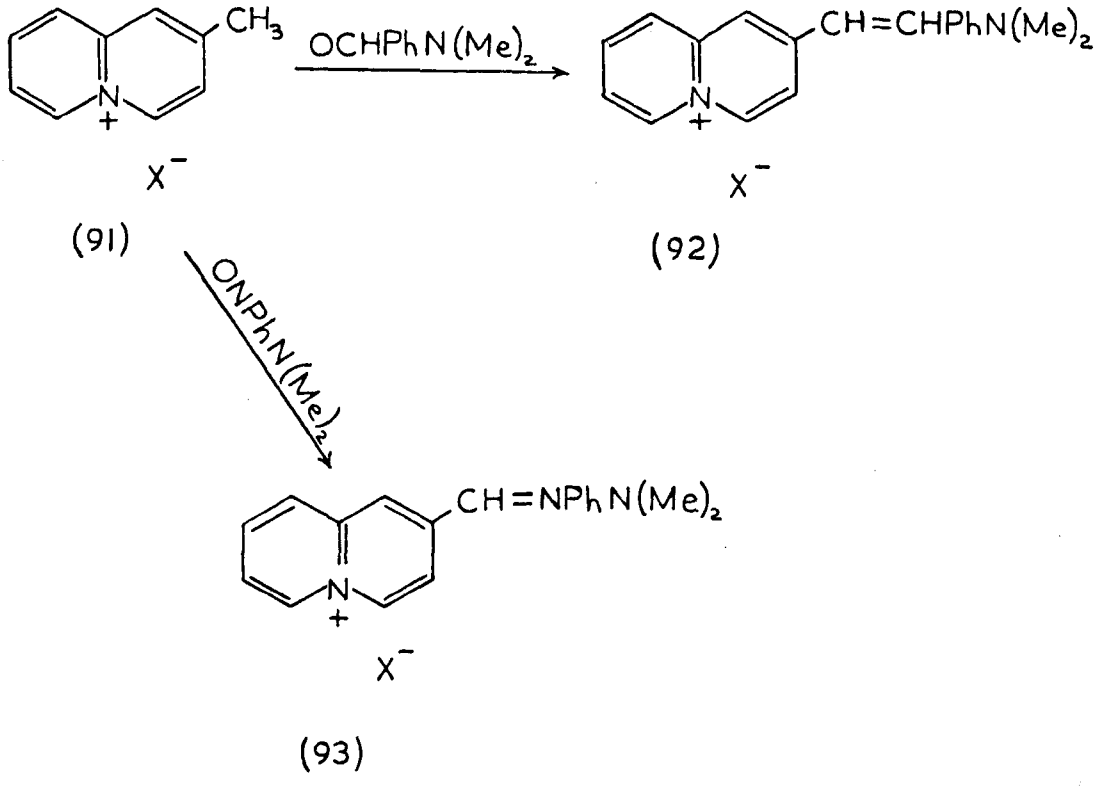
Under the same conditions, 2- and 3-hydroxyquinolizinium bromides have been shown to brominate in positions 1 and 4, respectively, but without simultaneous nitration. Apart from their studies on the substitution reactions of hydroxy-quinolizinium salts, Fozard and Jones[30,31,35] have led a general investigation into the properties of 1-, 2- and 3-hydroxy-quinolizinium salts and together with the work of Boekelheide and Lodge[36] and Boekelheide and Gall[46] on 4-hydroxyquinolizinium compounds, it has been established that these compounds show some analogy with the corresponding hydroxy pyridines. Thus, 1- and 3-hydroxyquinolizinium saltsin behaviour are typically phenolic, producing coloured solutions with aqueous ferric chloride and undergoing coupling reactions with aniline giving azo-dyes. 2- and 4-hydroxyquinolizinium salts behave more as quinolizones, but the ultraviolet absorbtion spectra and the properties of these compounds

suggest they are resonance hybrids to which the corresponding hydroxy zwitterions are major contributors. Thus both isomers produce coloured solutions with aqueous ferric chloride and form salts with picric acid and hydrochloric acid, though these are very unstable. As the quinolizones both the 2- and 4- compounds form the corresponding thioquinolizones on treatment with phosphorus pentasulphide and these are converted to methylmercaptoquinolizinium salts by methyl iodide. Van Allan and Reynolds[47] have reacted phosphorus oxychloride with 4-quinolizone (88) and obtained a good yield of 4-chloroquinolizinium dichlorophosphate (89) which on treatment with piperidine yields 4-piperidinoquinolizinium dichlorophosphate (90).



(88) (89) (90)

The methyl salts of the quinolizinium ion also show some analogy with the corresponding methyl pyridines. Richards and Stevens[12] have successfully condensed 2-methylquinolizinium salt (91) with p-dimethylamino benzaldehyde and with N,N-dimethyl-p-nitrosoaniline giving the compounds (92) and (93) respectively. 4-Methylquinolizinium bromide undergoes similar condensation with N,N-dimethyl-4-nitrosoaniline.[48]



Similar condensations are reported by Schultze and Willitzer.[49]

SYNTHESES OF 1- AND 2-AMINOQUINOLIZINIUM SALTS

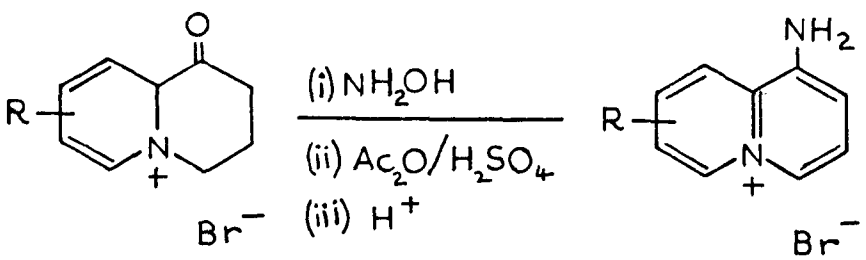
Introductory Remarks

The introduction to this thesis made reference to the electrophilic substitution reactions of 1-, 2- and 3-hydroxyquinolizinium salts by Fozard and Jones[30,31,35]. The reaction of 1-aminoquinolizinium salt with nitrous acid has been reported by Collicut and Jones[39] as having an electrophilic mechanism. In order to confirm these observations and possibly extend the scope of these electrophilic reactions of quinolizinium salts containing electron-donating groups, a number of 1- and 2-aminoquinolizinium salts have been made. This section deals with their syntheses and later an account of their properties is given.

****

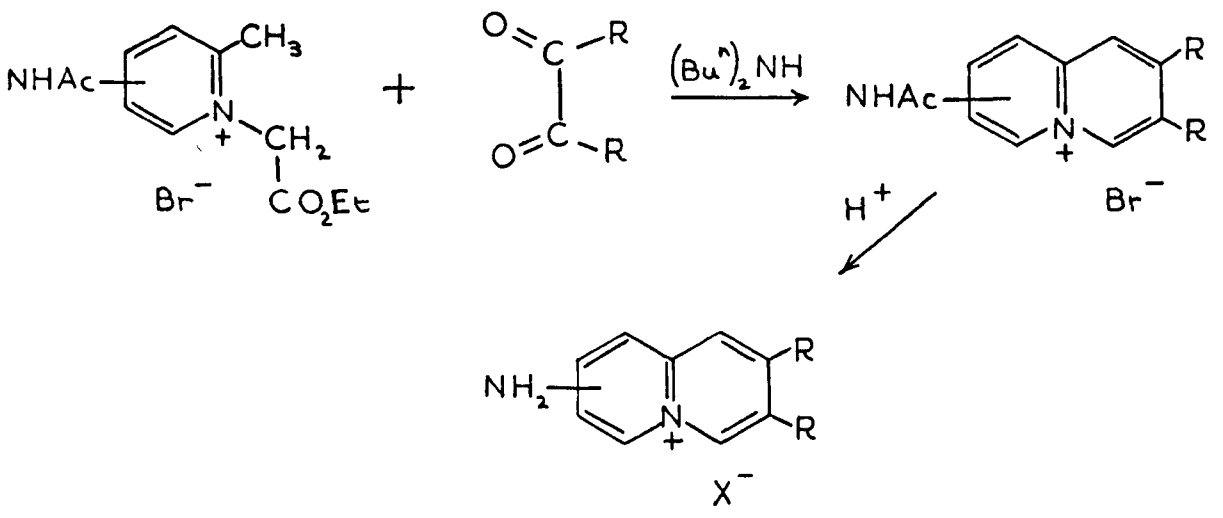
Discussion

The literature contains no general synthesis of aminoquinolizinium salts. The Collicut and Jones[39] synthesis of 1-aminoquinolizinium salt, as originally reported, offered a general synthesis of substituted 1-amino compounds (95) by starting with the appropriate substituted cyclic ketone (94). However, since the Wolff aromatisation when performed on a large scale[40] produced isomeric amino-hydroxy compounds, the method was unsatisfactory.



(94) (95)

As a general synthesis of di-substituted quinolizinium salts the Westphal, Jahn and Heffe[26] synthesis had been widely applied and by using appropriate acetamido 2-picolinium compounds, offered a route to aminoquinolizinium salts (96).



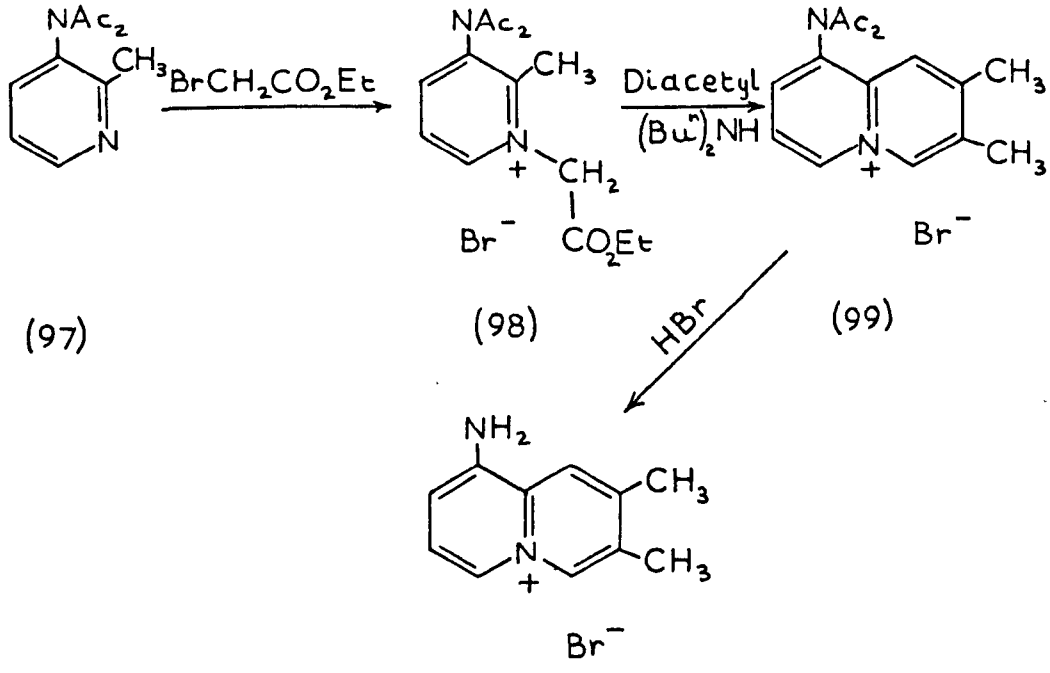
(96)

The authors[26] reported the synthesis of a number of quinolizinium salts unsubstituted in the 4-position when ethyl bromoacetate was used as the quaternising reagent. It was desirable, therefore, to employ the same reagent in the above scheme. Apart from the consistently high yields which had been obtained, the method had the advantage that the presence of the di-substituted groups would make for simpler interpretation of the nuclear magnetic resonance spectra of the amines and their electrophilic reaction products.

(a) Attempted synthesis of 1-amino-7,8-dimethylquinolizinium bromide (100)

The synthesis of this 1-aminoquinolizinium compound, using the Westphal method, was to be achieved by first preparing the diacetyl derivative of 3-amino-2-picoline (97). Reacting this compound (97) with ethyl bromoacetate would give the quaternary salt 3-diacetylamino--2-methyl-1-carbethoxymethylpyridinium bromide (98) which on cyclisation with diacetyl in the presence of di-n-butylamine would give 1-diacetylamino-7,8-dimethylquinolizinium bromide (99). Acid hydrolysis

of this amide (99) would then give 1-amino-7,8-dimethylquinolizinium bromide (100).

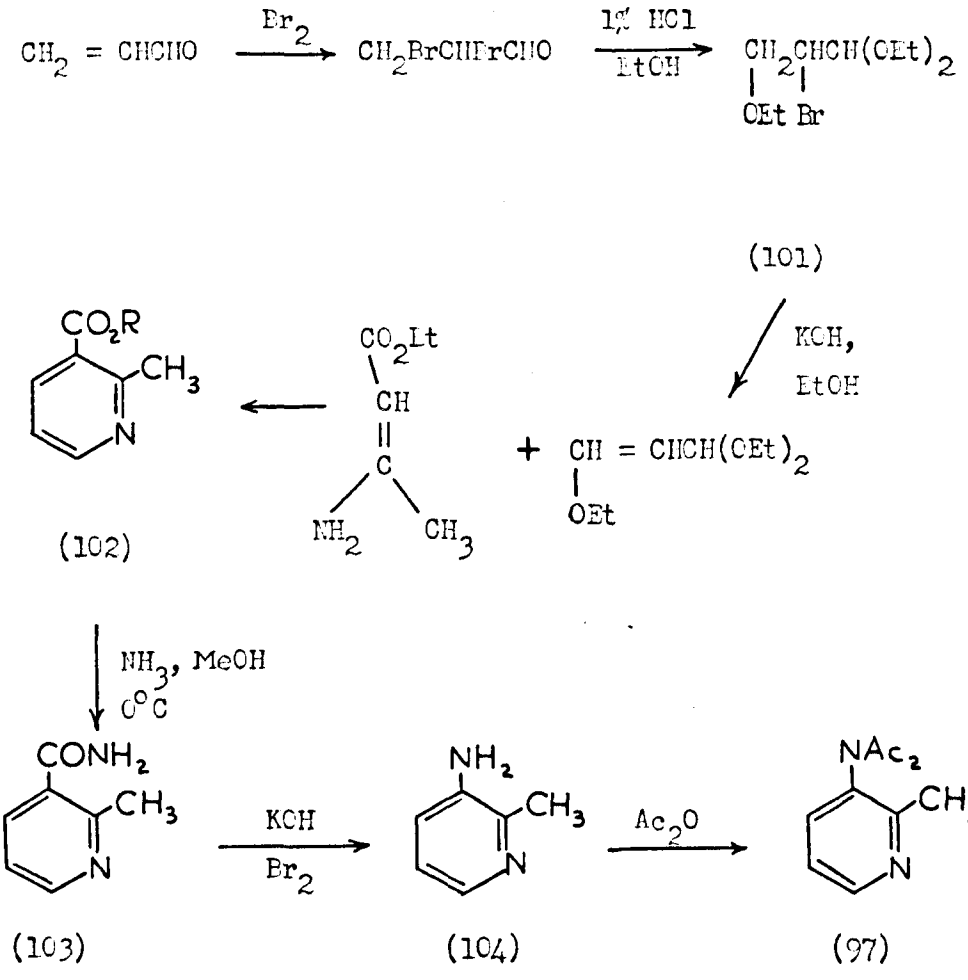


(97) (98) (99)

(100)

3-Diacetylamino-2-picoline was prepared as follows:

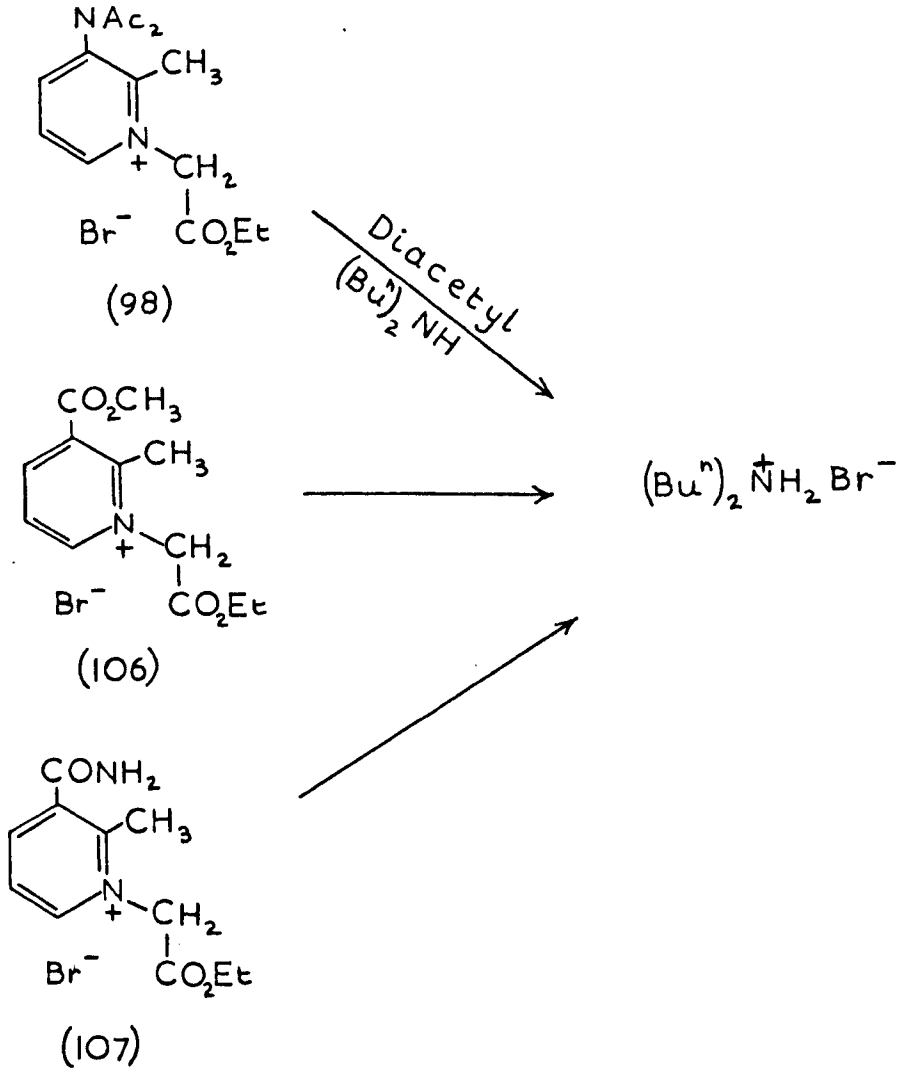
1,2-dibromopropanal was obtained by brominating acrolein and formed the 3-ethoxy diethylacetal (101) in refluxing ethanolic hydrogen chloride.[50] The acetal (101) was dehydrobrominated[51] in an ethanolic solution of potassium hydroxide and the product condensed with ethyl 3-aminocrotonate giving ethyl 2-methylnicotinate[52] (102, R = Et). The ester (102, R = Et), in methanolic ammonia, gave 2-methylnicotinamide[53] (103) which underwent Hofmann degradation to 3-amino-2-picoline[53] (104). On boiling the amine (104) in acetic anhydride, 3-diacetylamino-2-picoline (97) was obtained.[54]



The literature preparation[53] of 2-methylnicotinamide (103), by the action of methanolic ammonia on ethyl 2-methylnicotinate (102, R = Et) was found to proceed in small yield at 0°. When the reaction was repeated at 100° in an autoclave the amide (103) was again produced in small yield and the major product was the methyl ester (102, R = Me) of 2-methylnicotinic acid. A trans-esterification reaction was avoided by performing the reaction in ethanol, but at the elevated temperature in the autoclave, the yield was again small (3%). The yield improved to 74%, however, when

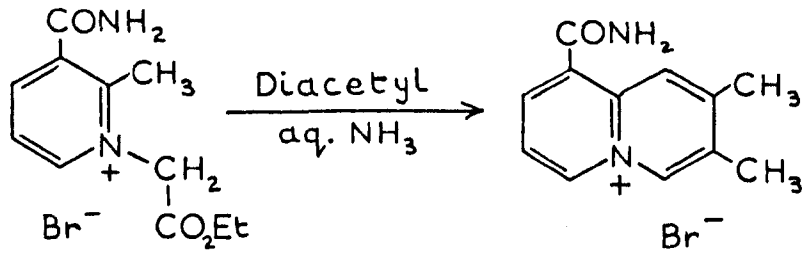
the methyl ester (102, R = Me) was treated with methanolic ammonia under the same conditions.

The diacetyl derivative (97) of 3-amino-2-picoline quaternised readily with ethyl bromoacetate in refluxing ethanol. Under the normal conditions of the Westphal synthesis, however, the resulting quaternary salt (98) failed to cyclise to a quinolizinium compound. When the salt



(98) was boiled with diacetyl and di-n-butylamine in ethanol the only isolable product was di-n-butylamine hydrobromide. The cyclisation was also unsuccessful when attempted on the quaternary salts (106) and (107) from methyl 2-methylnicotinate and 2-methylnicotinamide, respectively, and ethyl bromoacetate, di-n-butylamine hydrobromide again being produced.

Attempts to modify the synthesis by employing piperidine in place of di-n-butylamine as the catalyst, were unsuccessful when performed on the quaternary salt (107). Piperidine hydrobromide was isolated from the reaction. When dilute aqueous ammonia was used, however, the same quaternary salt (107) cyclised in 54% yield to 1-carbamoyl-7,8-dimethyl-quinolizinium bromide (108). This modification, though, was unsuccessful when applied to the pyridinium ester (106).



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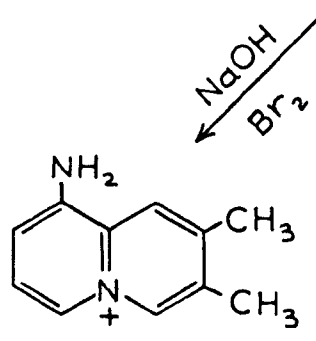
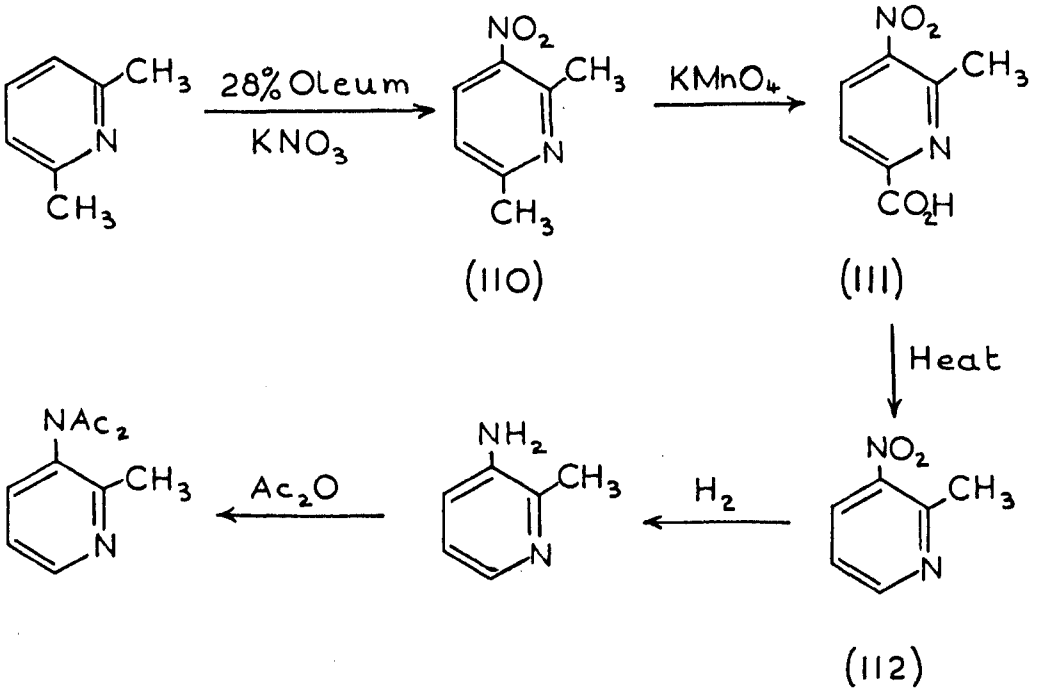


(109)

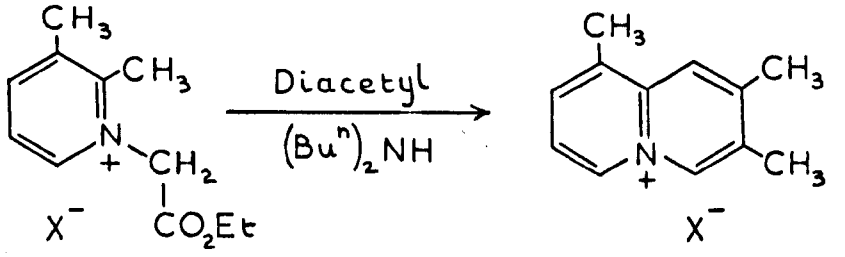
Attempts were made to convert the carbamoyl compound (108) to 1-amino-7,8-dimethylquinolizinium salt (109) by Hofmann degradation. From the reaction mixture it was possible to isolate a crude organic compound with no carbonyl absorption in the infrared spectrum and although this was presumed to be the amine (109), its highly impure form has prevented analytical verification.

Further attempts to prepare 1-amino-7,8-dimethylquinolizinium salt (109) from the diacetylamino pyridinium salt (98) using dilute aqueous ammonia in the cyclisation have been prevented due to a lack of 3-diacetylamino-2-picoline (97) as starting material. As an alternative synthesis of this compound it was proposed to nitrate 2,6-lutidine, oxidise the 6-methyl group of the resulting 3-nitro-2,6-lutidine (110) and decarboxylate the acid (111) to 3-nitro-2-picoline[55] (112). Reduction of this nitro-compound (112) followed by acetylation would then give 3-diacetylamino-2-picoline[54] (97).



Under the conditions reported in the literature,[55] the acid (111) decarboxylated in poor yield, predominantly with carbonisation. Attempted decarboxylations in high boiling solvents were also unsuccessful.

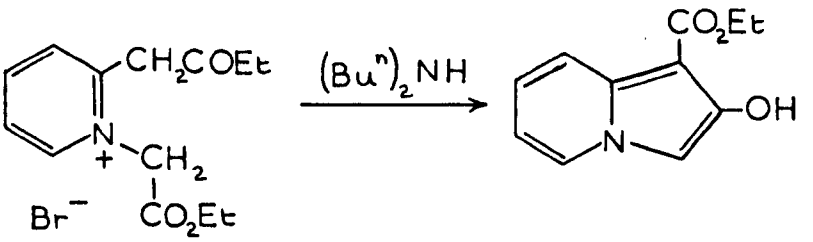
Although the work of Westphal[26] et al. and Wander[27] does not include the synthesis of 9-substituted quinolizinium compounds, it seems unlikely that the cyclisations of the quaternary salts (98), (106) and (107) are sterically inhibited by the substituents in the 3-position of the pyridinium systems. This view is upheld by the successful cyclisation of the quaternary salt (107) to the carbamoyl compound (108) using dilute aqueous ammonia, and is confirmed by the fact that the quaternary salt (113, X = Br) from 2,3-lutidine and ethyl bromoacetate cyclised to 1,7,8-trimethylquinolizinium bromide (114, X = Br) under the standard conditions of the Westphal synthesis.



(113) (114)

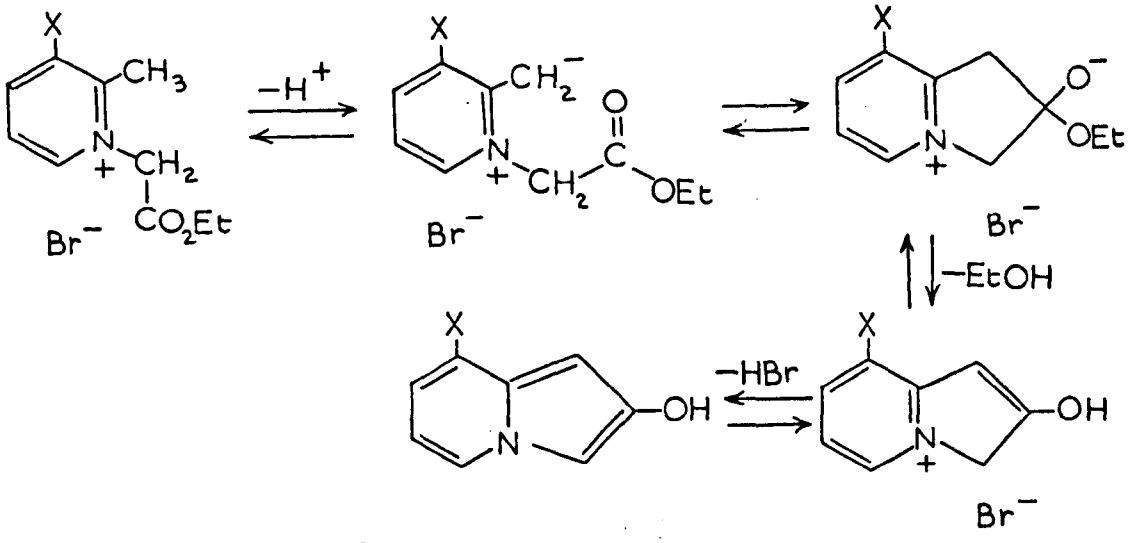
The formation of di-n-butylamine hydrobromide is the significant feature of these reactions and is attributed to an intra-molecular cyclisation leading to an indolizine. The determining factor is considered to be the reactivity of the 2-methyl group in the pyridinium

salt. The evidence in support of this view was obtained from studies on the cyclisation of the quaternary salt (115) from ethyl 2-pyridylacetate and ethyl bromoacetate. With two very active methylene groups this compound would appear most likely to condense with diacetyl. The only products isolated from the reaction of this quaternary salt (115) with diacetyl and di-n-butylamine, however, were di-n-butylamine hydrobromide and 1-carbethoxy-2-hydroxyindolizine (116), first prepared by Bragg and Wibberley.[56] The indolizine (116) was obtained in 75% yield by the action of di-n-butylamine alone on the quaternary salt (115).



(115) (116)

It seems likely that the effect of an electron-withdrawing group in position 3 of the quaternary salt would be to enhance the reactivity of the 2-methyl substituent sufficiently to allow condensation to occur with the ester-carbonyl function:-

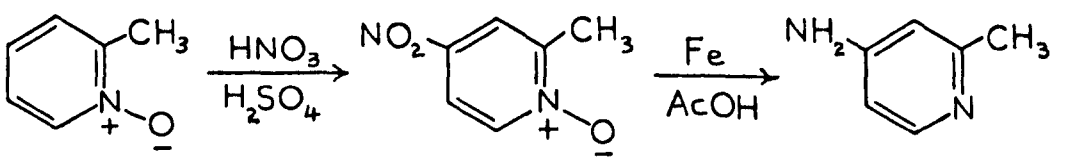


X = $-CONH_2$, $-CO_2Et$, $-N(Ac)_2$

Assuming close proximity between the 2-methyl group and the ester-carbonyl, intra-molecular condensation would compete successfully with inter-molecular condensation.

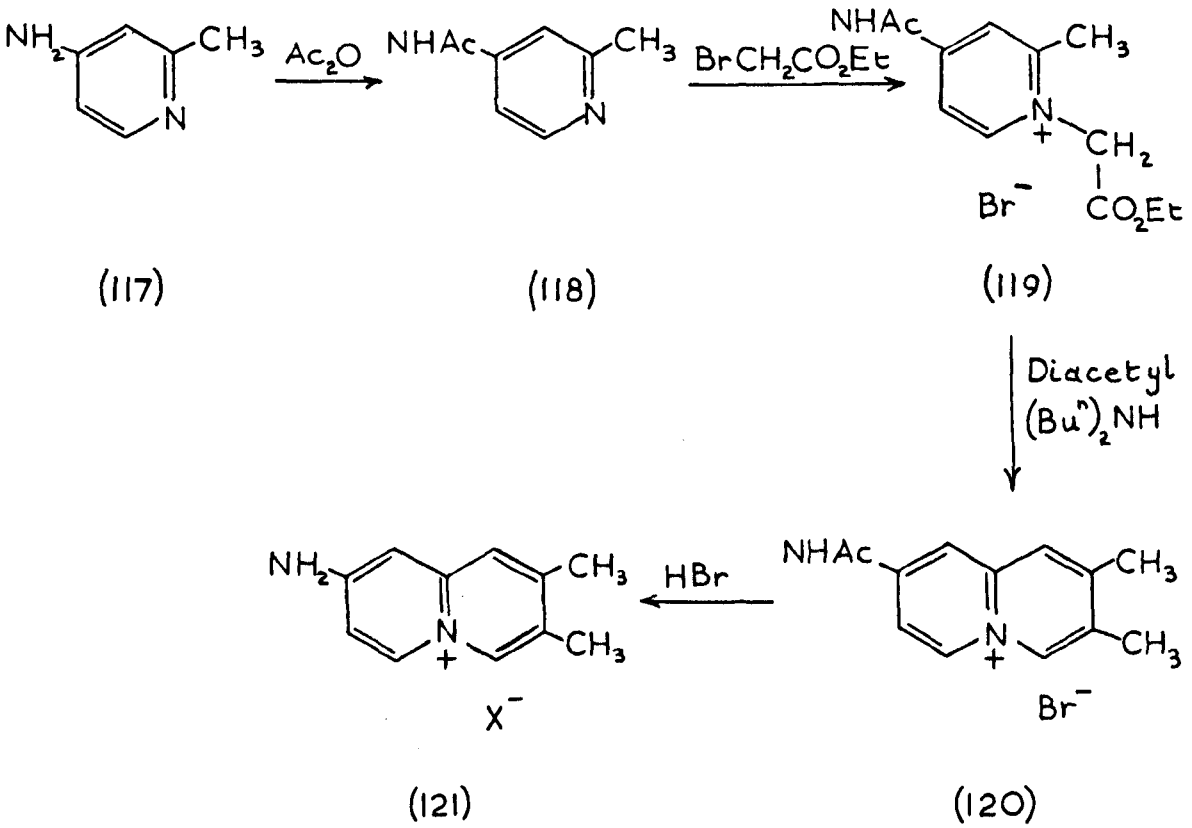
(b) Syntheses of 2-amino-7,8-dimethyl and 7,8-diphenylquinolizinium salts.

In order to examine further the effects of substituents on the cyclisation of pyridinium salts by the Westphal synthesis, 4-acetamido-2--picoline (118) was prepared. 4-Nitro-2-picoline-N-oxide was obtained by nitrating 2-picoline-N-oxide[57] and reduced to 4-amino-2-picoline (117) by iron filings and acetic acid.[58]



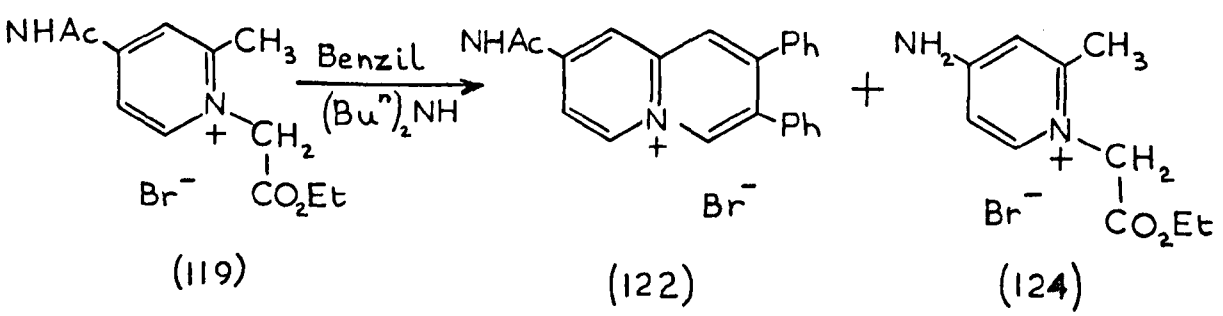
(117)

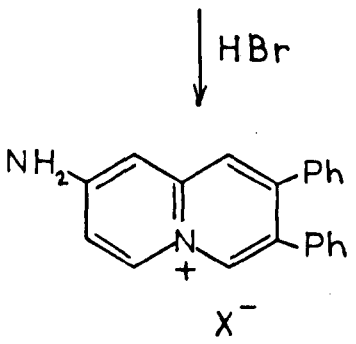
The amine (117) was acetylated to the hitherto unknown acetyl derivative (118) by boiling in acetic anhydride. The acetamido compound (118) quaternised readily with ethyl bromoacetate in refluxing ethanol giving 4-acetamido-2-methyl-1-carbethoxymethylpyridinium bromide (119). Cyclisation of this quaternary salt (119) with diacetyl and di-n-butylamine in refluxing ethanol gave 2-acetamido-7,8-dimethylquinolizinium bromide (120) in 73% yield. The acetamido quinolizinium salt (120) was hydrolysed to 2-amino-7,8-dimethylquinolizinium bromide (121, X = Br) in refluxing hydrobromic acid.



When attempts were made to cyclise the quaternary salt (119) with benzil and di-n-butylamine, two compounds were obtained from the reaction. One was the expected 2-acetamido-7,8-diphenylquinolizinium bromide (122)

isolated in 66% yield by crystallisation from water. Acid hydrolysis of this compound (122) gave 2-amino-7,8-diphenylquinolizinium bromide (123, X = Br). The other component was produced in small yield and was water-soluble. Its nuclear magnetic resonance spectrum showed it to be a pyridinium salt with one unsplit methyl group. The compound analysed as 4-amino-2-methyl-1-carbethoxymethylpyridinium bromide (124) and its structure was confirmed by the infrared spectrum which showed strong absorption at 1650 cm.$^{-1}$, characteristic of 4-aminopyridinium salts.

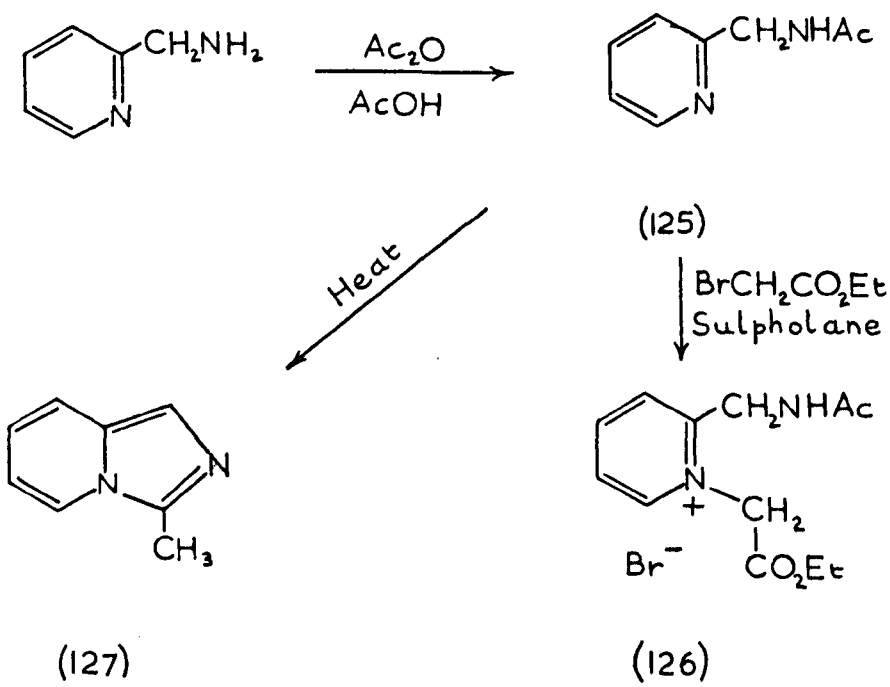




The amino-pyridinium salt (124) was also obtained by boiling the 4-acetamido quaternary salt (119) in ethanol with di-n-butylamine, but the compound (124) was recovered unchanged when cyclisation was attempted with benzil and di-n-butylamine.

(c) Syntheses of 1-amino-2,3-dimethyl and 2,3-diethylquinolizinium salts.

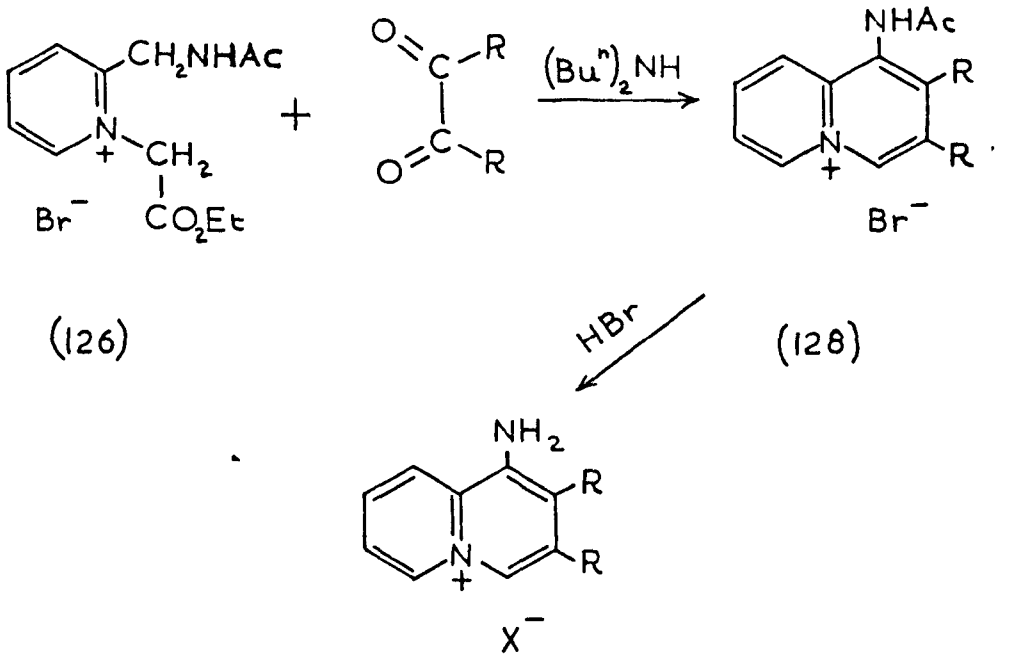
The synthetic method was applied with further success to the synthesis of 1-amino-2,3-di-substituted quinolizinium compounds starting from 2-picolylamine. Acetylation in a mixture of acetic acid and acetic anhydride gave 2-acetamidomethylpyridine[59] (125). The quaternary salt (126) of the amide (125) was prepared by treatment with ethyl bromo-acetate in sulpholane at 35°C. The usual method of quaternising in refluxing ethanol was not applied because of the tendency of the acetamido compound (125) to cyclise to the aza-indolizine (127) on prolonged heating.[59]



(127) (126)

The quaternary salt (126) was obtained as an oil but cyclised in refluxing ethanol to 1-acetamido-2,3-dimethyl (128, R = CH_3), and 1-acetamido-2,3-diethylquinolizinium bromides (128, R = Et) with diacetyl and dipropionyl, respectively, using di-n-butylamine as the

catalyst. The yields were 54 and 41%, respectively, based on 2-acetamidomethylpyridine as starting material. Both of these acetamido compounds hydrolysed to the corresponding amines (129, R = CH_3, Et, X = Br) in refluxing hydrobromic acid.

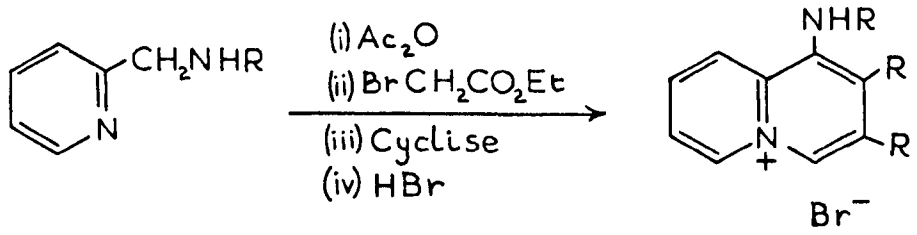


(126) (128)

(129)

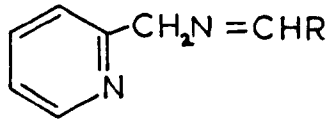
(d) Attempted synthesis of 1-benzylamino-2,3-dimethylquinolizinium bromide (131, R = CH_2Ph)

By suitably modifying the above syntheses of 1-amino-2,3-disubstituted quinolizinium salts it was proposed to synthesise a secondary 1-amino-2,3-disubstituted quinolizinium compound (131) starting from a secondary 2-aminomethylpyridine (130).

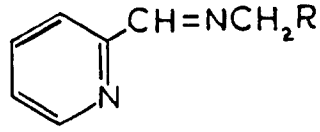


(130) (131)

As an initial approach, the synthesis and reduction of a Schiff's base of the type (134) was investigated.

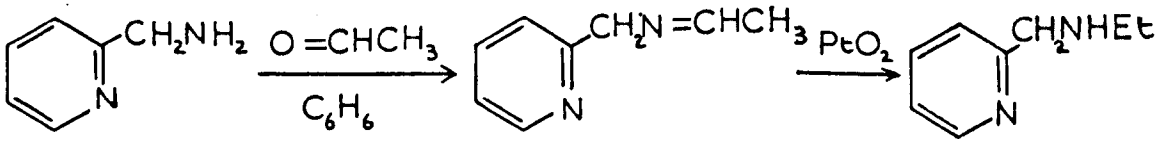


(134)



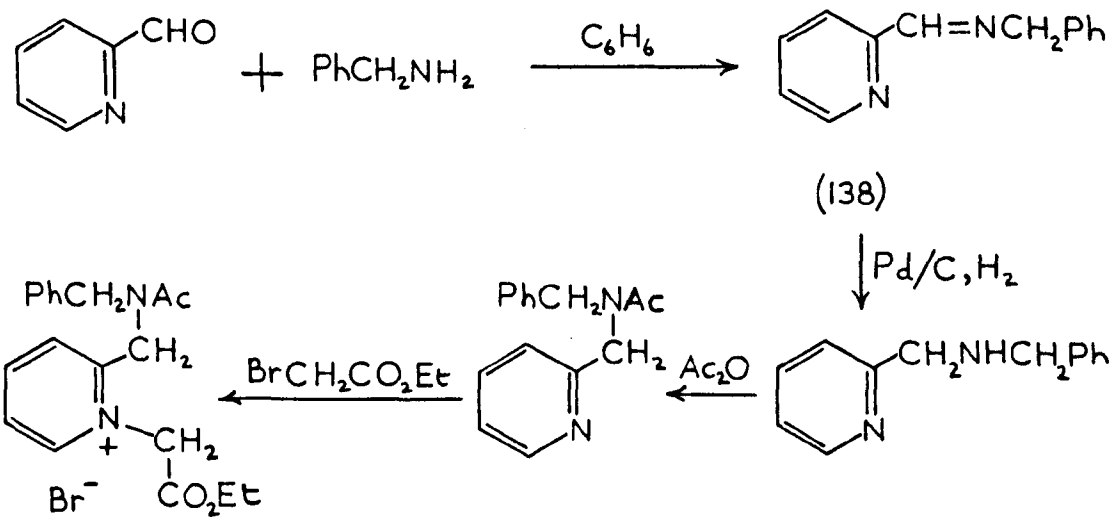
(135)

By condensing acetaldehyde with 2-picolylamine it was hoped to prepare N-(2-pyridylmethyl)acetaldimine (136). The reaction at room temperature in benzene, however, gave a mixture of the aldimine (136) and 2-picolylamine and only by reduction of the mixture was it possible to separate the primary amine by distillation. The other component of the reduced mixture was 2-ethylaminomethylpyridine (137), but the yield was too small to permit further investigation along this line.

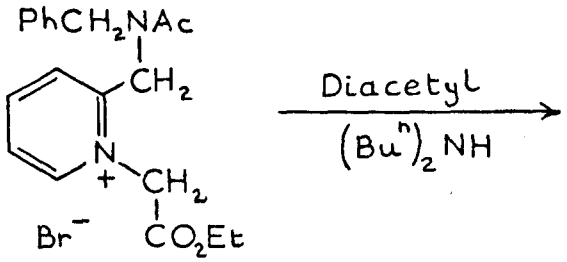


(136) (137)

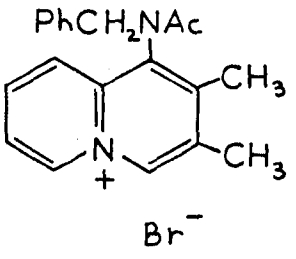
The synthesis of a Schiff's base of the type (135) was more successful. In this case pyridine-2-aldehyde was condensed with benzylamine in benzene. The water formed during the reaction was azeotroped using a Dean-Stark apparatus and distillation of the evaporated benzene solution gave N-benzyl-pyridine-2-aldimine (138) in 82% yield. The aldimine (138) was reduced with palladium charcoal and hydrogen to 2-benzylaminomethylpyridine (139) in 91% yield and acetylation gave 2-N-benzylacetamidomethylpyridine (140) in 90% yield. The quaternary salt (141) of the acetamido compound (140) was obtained by treatment with ethyl bromoacetate in sulpholane.



An ethanolic solution of the quaternary salt (141) cyclised with diacetyl using di-n-butylamine as the base. The product, however, was not the expected 1-N-benzylacetamido-2,3-dimethyl quinolizinium bromide (142), but the N-benzylacetamido ester (143), obtained in 21% yield based on 2-N-benzylacetamidomethylpyridine (140) as starting material.



(141) (143)

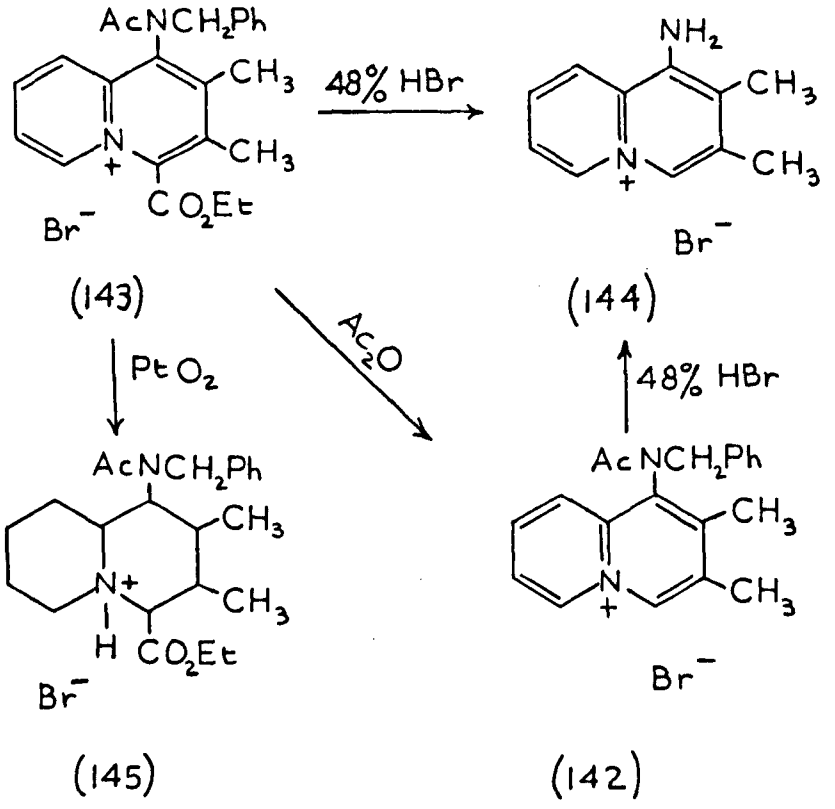


(142)

In previous cases where simple pyridinium salts were used, cyclisation proceeded with loss of the carbethoxy group from position 4 of the quinolizinium salt. It seems likely that the ester is intermediate in these reactions and is readily hydrolysed and decarboxylated even under the mild conditions of the reactions. The N-benzylacetamido ester (143), however, was resistant to prolonged boiling in alcoholic solutions of di-n-butylamine, basic resin and aqueous solutions of ammonia and lithium hydroxide. The ester (143) was also recovered unchanged after prolonged boiling in concentrated hydrochloric acid, but boiling in 48% hydrobromic acid for 1 hour removed the ester, acetyl and benzyl group giving 1-amino-2,3-dimethylquinolizinium bromide (144) obtained previously by the hydrolysis of 1-acetamido-2,3-dimethylquinolizinium bromide (128, R = CH_3). Considering the ease with which the

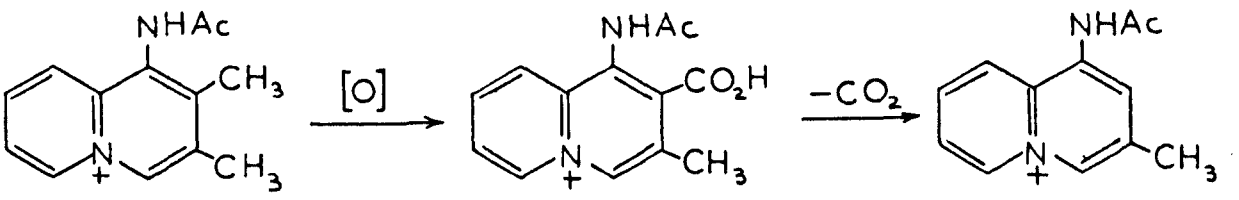
benzyl group was cleaved by hydrobromic acid, it was surprising that it was not removed by catalytic reduction with platinum oxide as an N-benzylacetamidoquinolizidine hydrobromide (145) was obtained.

It seems likely that removal of the ester group is largely temperature--dependent for the N-benzylacetamido-2,3-dimethyl compound (142) was obtained from the ester (143) by refluxing in acetic acid overnight or, better still, in acetic anhydride for a few hours giving an 87% yield of (142). It was not possible, however, under any of the conditions tried, to deacetylate the N-benzylacetamido compound (143) without also removing the benzyl group giving 1-amino-2,3-dimethylquinolizinium bromide (144).



(e) Synthesis of 1-amino-3-methylquinolizinium bromide (167).

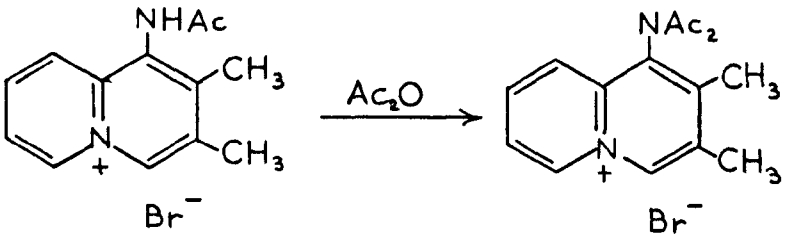
During the course of the research it was necessary to prepare an amino quinolizinium salt unsubstituted by a methyl group in the 2- or 8-position of the quinolizinium system. As originally reported, the Westphal synthesis was applicable to the preparation of 2,3- or 7,8-substituted compounds and only by the oxidation of the 2- or 8-methyl substituent did it seem possible to obtain a mono-methyl amino quinolizinium salt. Thus, initial attempts were directed at oxidising the 2-methyl group of 1-acetamido-2,3-dimethylquinolizinium bromide (146) and decarboxylating the resulting acid, 1-acetamido-2--carboxy-3-methylquinolizinium bromide (147), to 1-acetamido-3-methyl-quinolizinium bromide (148).



(146) (147) (148)

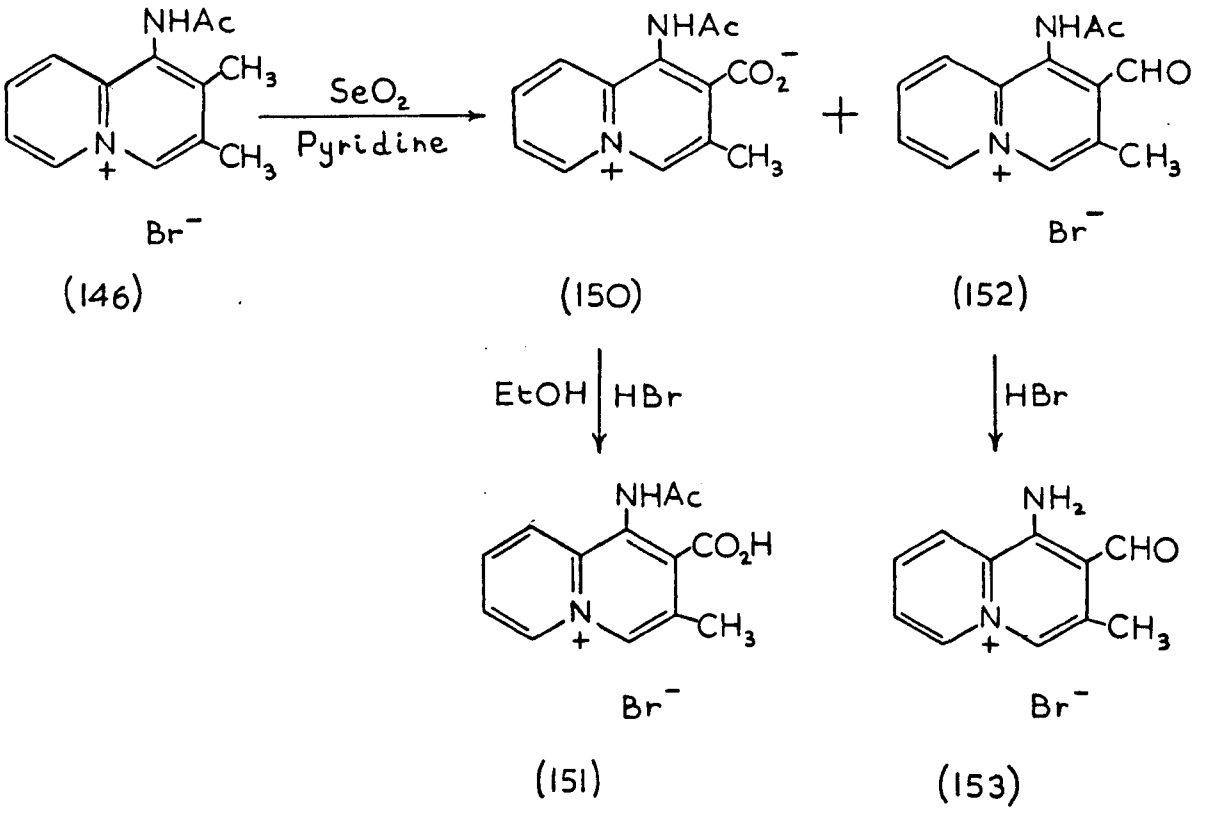
The literature contains a number of references to the oxidation of alkyl pyridines and quinolines by selenium dioxide[60,61] and potassium permanganate.[62,55] For practical reasons selenium dioxide was chosen as the oxidising agent for the quinolizinium compound (146). From the range of solvents commonly used in selenium dioxide oxidations, ethanol, acetic anhydride and pyridine were the most convenient to use. Of these, the latter two were least convenient because of solubility problems.

When ethanol was employed as solvent, the 1-acetamido compound (146) failed to oxidise over prolonged periods of boiling, starting material being recovered. When acetic anhydride was used, the diacetyl derivative (149) of 1-amino-2,3-dimethylquinolizinium bromide was obtained. This compound was not formed under oxidative conditions as it was also produced in quantitative yield by boiling in acetic anhydride alone.



(146) (149)

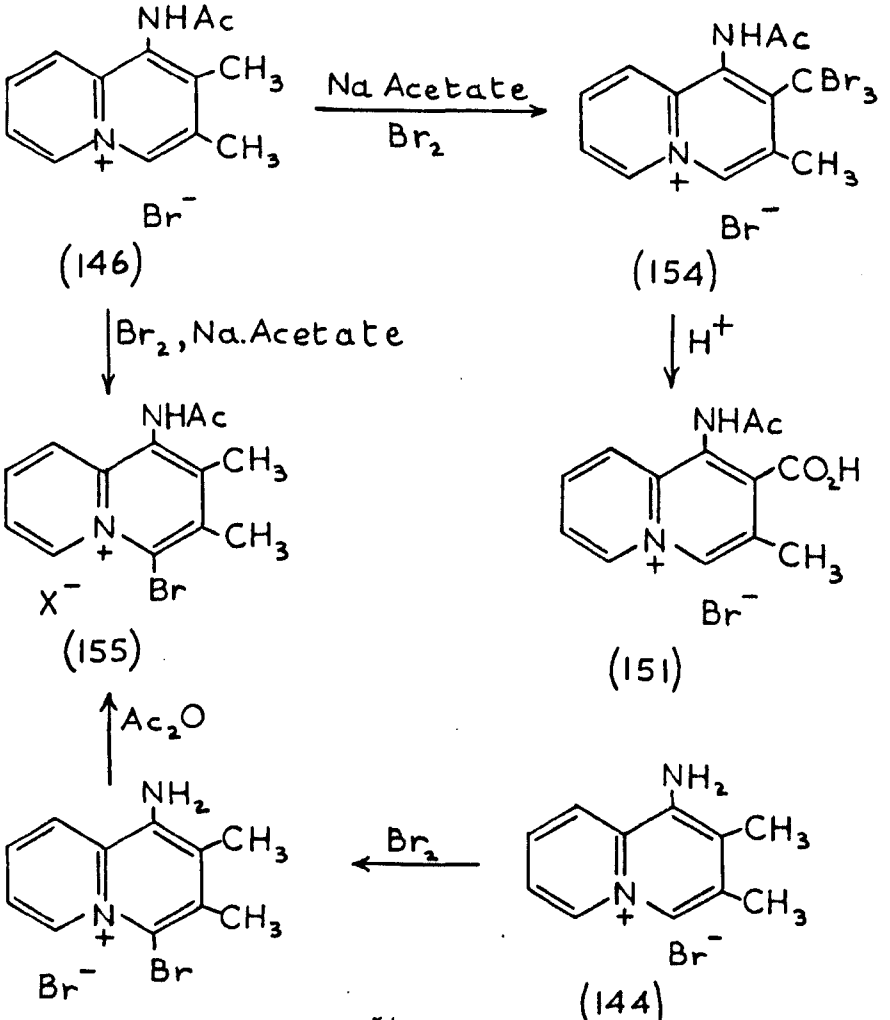
When the reaction was repeated in pyridine,n-butanol was added to the reaction mixture to increase the solubility of the acetamido compound. From the reaction, two quinolizinium compounds were obtained. One crystallised from the refluxing solution and was assumed to be the carboxylate (150) of 1-acetamido-2-carboxy-3-methylquinolizinium bromide (151); the free acid was obtained in 35% yield by recrystallising the carboxylate (150) from alcohol containing hydrobromic acid. The other product was the aldehyde (152) which precipitated from the evaporated solution in 33% yield and was identified by hydrolysis to the highly crystalline 1-amino-2-formyl-3-methylquinolizinium bromide (153).



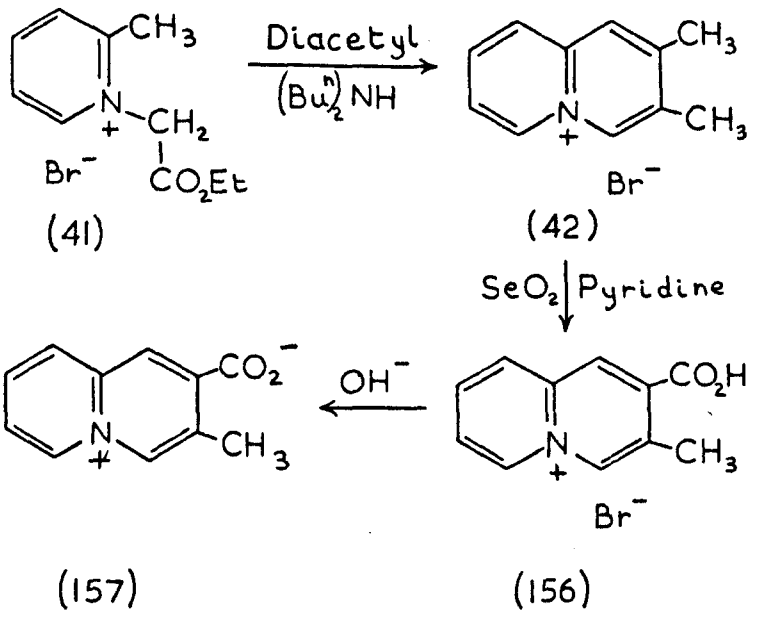
Although the aldehyde (152) was assumed to be intermediate in the oxidation to the carboxylate (150), attempts to oxidise the 2-methyl group completely to the carboxylate group were unsuccessful. When the reaction was repeated using excess selenium dioxide and increasing the reflux time, the two products were always obtained in the same proportions. Attempts to oxidise the aldehyde (152) to the carboxylate (150) under the same conditions gave no purifiable material. Other unusual oxidation reactions with selenium dioxide are reported in the literature.

As an alternative approach, a method described for the oxidation

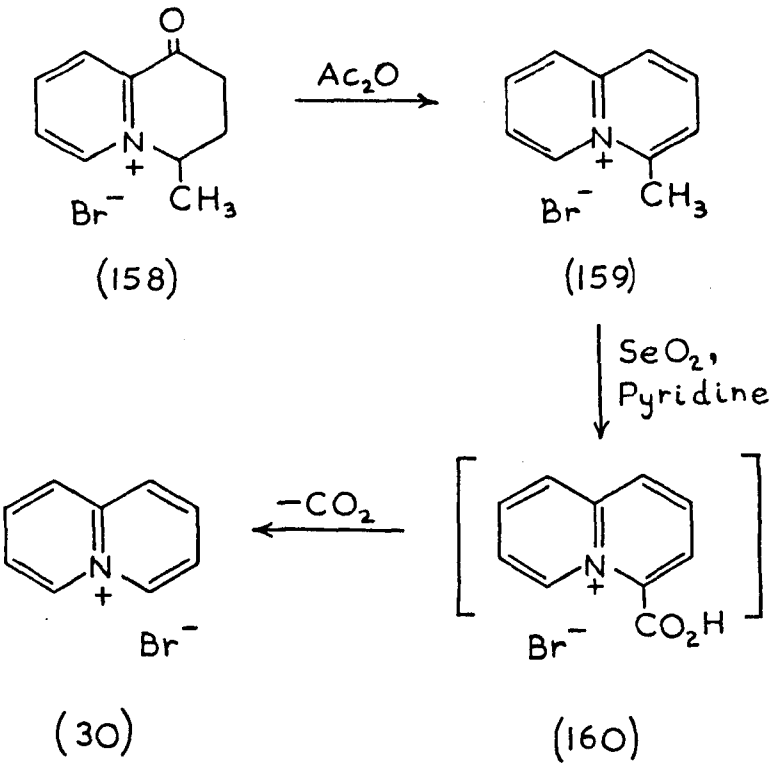
of methyl lepidine was considered.[63] By brominating the 2-methyl group of the 1-acetamido compound (146), the tribromo-compound (154) would be obtained and acid hydrolysis would give the acid (151). Bromination was attempted in a hot aqueous solution of sodium acetate. From the cooled solution was obtained an oil which solidified from an evaporated solution of alcohol and acetone in 23% yield. The product was identified as 1-acetamido-2,3-dimethyl-4-bromoquinolizinium bromide (155, X = Br). This compound was also obtained by the bromination and then acetylation of 1-amino-2,3-dimethylquinolizinium bromide (155). Details of this synthesis are given later.



The anomolous behaviour of the 1-acetamido compound (146) under the oxidative conditions with selenium dioxide was not shown by simpler quinolizinium salts. 2,3-Dimethylquinolizinium bromide (42) was prepared[26] by cyclising 2-methyl-1-carbethoxymethylpyridinium bromide (41) with diacetyl and oxidised directly to 2-carboxy-3-methylquinolizinium bromide (156) in 68% yield without the isolation of an intermediate aldehyde. On treatment with basic resin the carboxylate (157) was obtained.

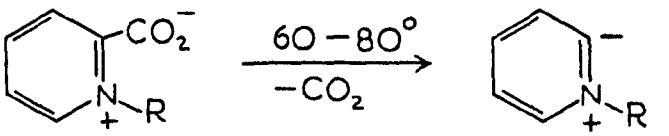


4-Methylquinolizinium bromide (159) was obtained by aromatising 1-oxo--4-methyl-1,2,3,4-tetrahydroquinolizinium bromide (158) in boiling acetic anhydride[16] and oxidised under the usual conditions to quinolizinium bromide (30) in 66% yield. 4-Carboxyquinolizinium bromide (160) is presumed to be an intermediate in this reaction.

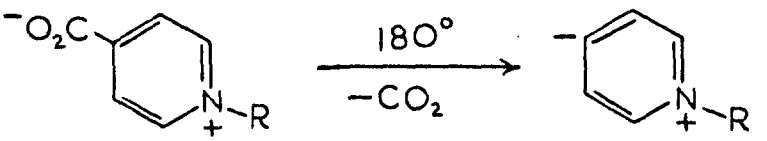


The purification of the 2-carboxy-3-methyl salt (156) was considerably easier than that of the 1-acetamido-2-carboxy compound (151) and was used as a model in attempts to discover the best method of decarboxylating the two acids. Under a variety of conditions, the 2-carboxy compound (156) was found to be unusually resistant to decarboxylation. Boiling in hydrobromic acid, acetic acid and acetic anhydride failed to give the expected 3-methylquinolizinium bromide and only starting material was isolated. When the acid was heated at its melting point carbon dioxide was evolved but no purifiable material was isolated. The carboxylate (157) was equally resistant to decarboxylation. A recent publication[64] describes the ease with which 2- and 4-pyridinium carboxylates lose carbon dioxide. In the case of the 2-carboxylates (161), decarboxylation occurs by boiling in aprotic solvents at 60 to 80°C. The 4-carboxylates (162) similarly undergo decarboxylation but in

solvents boiling up to 100°C higher.

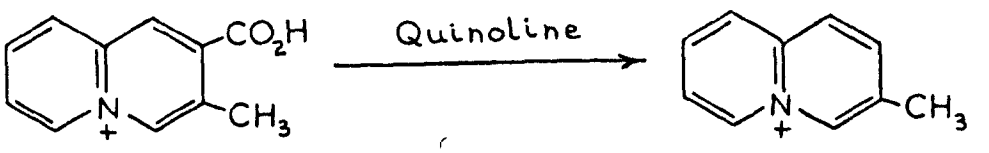


(161)



(162)

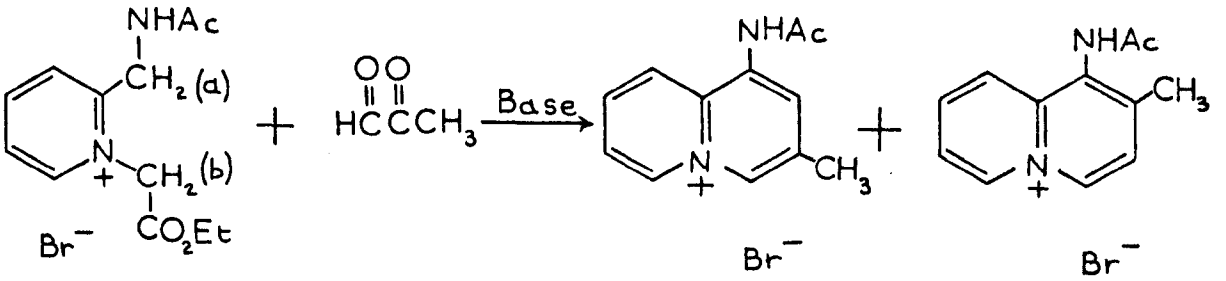
The quinolizinium carboxylate (157), however, did not decarboxylate in benzene, xylene, pyridine or ethylene glycol. From each reaction the 2-carboxy compound (156) was obtained after evaporation of the solvent and crystallisation from alcohol containing hydrobromic acid. The acid was finally decarboxylated in boiling quinoline with copper powder. The solvent was removed by steam distillation and 3-methylquinolizinium bromide (163) crystallised from the evaporated aqueous solution. The yield was poor, however, and a pure sample could be obtained only by repeated recrystallisation. The physical properties were the same as those reported in a previous synthesis.



(156) (163)

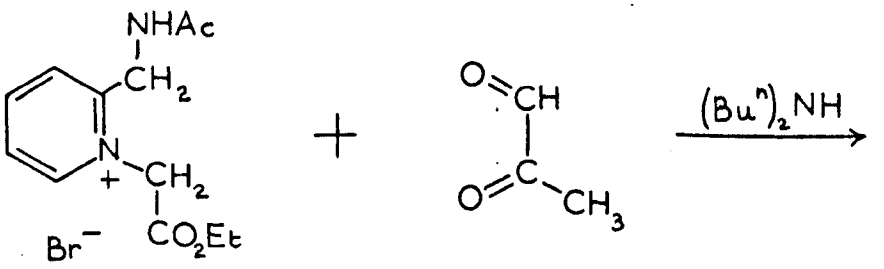
The same difficulties were encountered in attempts to decarboxylate the 1-acetamido-2-carboxy compound (151). The salt was recovered unchanged after boiling in a variety of solvents. When decarboxylation was attempted in boiling quinoline it was impossible to isolate a pure compound from the reaction.

Because of the difficulties involved in the decarboxylation of the above acids (156) and (151), attempts were directed at synthesising a 1-amino-3-methylquinolizinium salt by modification of the Westphal synthesis. Instead of using an α-diketone in the cyclisation of the quaternary salt 2-acetamidomethyl-1-carbethoxymethylpyridinium bromide (126), pyruvic aldehyde was employed. Although the reaction could have given either of the two isomeric acetamidoquinolizinium salts (164) and (165) or a mixture of both, the literature contains numerous references[65,66,67] to the condensation of aldehydes with the more active 2-methyl or 2-methylene function of a 2-substituted pyridinium salt and supported the view that cyclisation would give compound (164). The nuclear magnetic resonance spectrum of the quaternary salt (126) in deuterium oxide provided further support by confirming that the methylene hydrogen atoms (a) in the acetamidomethyl group were more active than those (b) in the carbethoxymethyl group since they exchanged much more rapidly with deuterium.

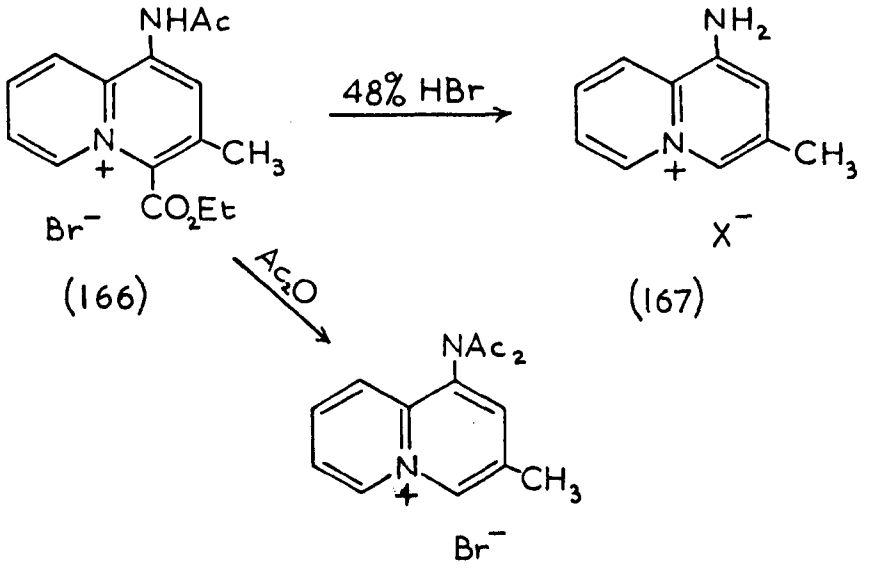


(126) (164) (165)

When an ethanolic solution of the quaternary salt (126) was boiled with a 40% aqueous solution of pyruvic aldehyde and di-n-butylamine, 1-acetamido-3-methyl-4-carbethoxyquinolizinium bromide (166) was obtained. The yield was 42%, based on 2-acetamidomethylpyridine as starting material. Hydrolysis of the acetamido-ester (166) in hydrobromic acid gave 1-amino-3-methylquinolizinium bromide (167, X=Br) in 89% yield with loss of the ester group. Boiling in acetic anhydride also caused decarboxylation giving 1-diacetylamino-3-methylquinolizinium bromide (168) in 77% yield.



(126)



(166) (167) (168)

The position of the methyl group in each of these quinolizinium salts was confirmed by comparing the nuclear magnetic resonance spectra of the amino-methyl compound (167, X=Br) and its diacetyl derivative (168) with those of 1-amino-2,3-dimethylquinolizinium bromide (144) and its diacetyl derivative (149). The aromatic regions of these spectra are shown on pages 122 and 123. The aromatic proton in position 6 of the dimethyl-diacetyl compound (149) appears as a doublet at 0.6τ and is superimposed on a singlet due to the proton in position 4. The proton in position 4 of the monomethyl-diacetyl compound (168) would be expected to appear as a doublet superimposed on that due to the proton in position 6. The doublet due to proton 4 would arise either from ortho-coupling with the proton in position 3 (2-methyl substituted)

or meta-coupling with the proton in position 2 (3-methyl substituted). The coupling constant would be significantly larger in the former than in the latter case. The spectrum of the compound (168), in fact, shows only an unresolved doublet, appearing as a broad singlet at 0.6τ, and confirms that the methyl group is substituted in position 3. Further evidence is provided by the spectrum of the monomethyl-amino compound (167,X=Br) which has two broad singlets, unresolved as doublets, at 1.9τ and 2.9τ due to protons 4 and 2, respectively.

The synthesis of quinolizinium salts using pyruvic aldehyde as the α-dicarbonyl reagent was limited to the preparation of the acetamido-ester (166). When cyclisations were attempted on the 2-methyl (41) and 4-acetamido-2-methyl (119)quaternary salts, no pure products were obtained.

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It is clear from the preceding discussion that the success of the Westphal synthesis to a large extent depends on the nature of the pyridinium salt. The type of reaction which occurs may be either an inter-molecular cyclisation, giving a quinolizinium salt, or an intra-molecular cyclisation, producing an indolizine. In most of the experiments one reaction took precedence over the other. In those reactions from which no pure materials were isolated,

the two cyclisations are presumed to take place at the same rate.

Under a given set of conditions, the type of substituent in the pyridinium salt affects the reactivity of the 2-methyl group and may determine which of the two cyclisations takes precedence. Thus, the effect of an electron-withdrawing group ($-CO_2Et$, $-CONH_2$, $-NAc_2$?) in position 3 of the salt, is to enhance the activity of the 2-methyl group sufficiently for intra-molecular cyclisation to occur. On the other hand, a strongly electron-donating group ($-NH_2$) in position 4, reduces the reactivity to such an extent that neither intra-molecular nor inter-molecular cyclisations occur. A less powerful electron-donating group (-NHAc) in position 4, has no effect on the activity of the 2-methyl group and cyclisation occurs inter-molecularly giving a quinolizinium salt. In one case it was possible to compensate for intra-molecular reaction by using a different base. When the amido-pyridinium salt (107) was reacted with diacetyl using di-n-butylamine, cyclisation occurred intra-molecularly, but when dilute aqueous ammonia was used a quinolizinium salt was obtained. It might therefore be possible to correlate the type of cyclisation with different bases.

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Experimental

Melting points were determined on a Kofler block and are uncorrected.

Infrared absorption spectra were measured with Perkin Elmer 257 and 221 spectrophotometers. The spectra of solids were determined as Nujol mulls, indicated as (Nujol). The spectra of liquids were determined as liquid films (film), or solutions (CCl_4).

Nuclear magnetic resonance spectra were recorded on a Perkin Elmer R10 60 megacycle instrument and are quoted in units of "tau" (τ) using a tetramethyl silane (T.M.S.) standard. When spectra were determined in deuterium oxide the T.M.S. standard was recorded externally in a solution of carbon tetrachloride. In all other cases the standard was used internally.

Ultraviolet spectra were determined on a Unicam SP 800 instrument.

Microanalyses were carried out by Drs. Weiler and Strauss of Oxford and Mr. J. Boulton of Keele University.

Acrolein Dibromide.

Prepared from acrolein by the method of Fischer and Giebe.[50]

3-Ethoxy-2-bromopropanal Diethyl Acetal,(101).

Prepared from acrolein dibromide also by the method of Fischer and Giebe.[50]

β-Ethoxyacrolein Diethyl Acetal

Prepared by the dehydrobromination of 3-ethoxy-2-bromopropanal diethyl acetal by the method of Price and Moos.[51]

Ethyl 2-methylnicotinate,(102, R = Et).

Prepared from β-ethoxyacrolein diethyl acetyl and ethyl 3-aminocrotonate by the method of Baumgarten and Dornow.[52]

2-Methylnicotinamide,(103).

The aminolysis of ethyl 2-methylnicotinate by the method of Dornow[53] gave a small yield of 2-methylnicotinamide (103). Treatment of ethyl 2-methylnicotinate with methanolic ammonia at 100°C in an autoclave also gave a poor yield, the main product being methyl 2-methylnicotinate (102, R = CH_3). A solution of 35 g. of methyl 2-methylnicotinate in 200 cc. of dry methanol was saturated with ammonia at 0°C. The solution was then heated at 100°C in an autoclave (15 atm. pressure) for 5 hours. The solvent was evaporated and the residue crystallised from ether and recrystallised from ethanol giving 23 g. (75%) of the amide (103), m.p. 159°C.

3-Amino-2-picoline,(104).

Prepared by Hofmann degradation of 2-methylnicotinamide.[53]

3-Diacetylamino-2-picoline, (97).

This compound was prepared by acetylating 3-amino-2-picoline by the procedure reported by Clemo and Swan.[54]

3-Diacetylamino-2-methyl-1-carbethoxymethylpyridinium Bromide, (98).

A solution of 3.6 g. of 3-diacetylamino-2-picoline (97) and 4.0 g. of ethyl bromoacetate in 40 ml. of ethanol was boiled under reflux for 5 hours. The solution was evaporated to dryness and the residue solidified in ethyl acetate. The solid residue crystallised from ethanol-ethyl acetate giving 2.0 g. (30%) of the quaternary salt (98) m.p. 81°.

$C_{14}H_{19}N_2O_4Br$ requires: C, 46.83, H, 5.33, N, 7.80%

Found: C, 46.5, H , 5.42, N, 7.7%

$\nu_{max.}$(Nujol) 1750 cm.$^{-1}$ (ester CO) 1695 cm.$^{-1}$ (acetyl CO).

3-Carbamoyl-2-methyl-1-carbethoxymethylpyridinium Bromide, (107).

5.0 g. of 2-methylnicotinamide (103) and 6.4 g. of ethyl bromoacetate were boiled for 5 hours in 40 ml. of ethanol. The solution was evaporated to dryness and the residue solidified in ethyl acetate. Crystallisation from ethanol-ethyl acetate gave 10.1 g. (91%) of the pyridinium salt (107), m.p. 201°.

$C_{11}H_{15}N_2O_3Br$ requires: C, 43.56, H, 4.99%

Found: C, 43.4, H, 4.75%

$\nu_{max.}$(Nujol) 1740 cm.$^{-1}$ (ester CO) 1690 cm.$^{-1}$ (amide CO).

3-Carbomethoxy-2-methyl-1-carbethoxymethylpyridinium Bromide, (106).

A solution of 4.0 g. of methyl 2-methylnicotinate (102, R = CH_3) and 4.7 g. of ethyl bromoacetate in 40 ml. of ethanol was boiled under reflux for 5 hours. The solution was evaporated to dryness and the residue solidified from ethyl acetate. Crystallisation from ethanol-ethyl acetate gave 3.0 g. (36%) of the quaternary salt (106), m.p. 120°.

$C_{12}H_{16}NO_4Br$ requires: C, 45.27; H, 5.07; N, 4.40%

Found: C, 45.3; H, 4.68; N, 3.9%

$\nu_{max.}$(Nujol) 1750 cm.$^{-1}$ (Et ester CO) 1730 cm.$^{-1}$ (Me ester CO)

1-Carbamoyl-7,8-dimethylquinolizinium Bromide, (108).

2.5 g. of 3- carbamoyl-2-methyl-1-carbethoxymethylpyridinium bromide (107) was boiled for 1 hour in 30 ml. of ethanol with 1.5 g. of diacetyl and 2 ml. of dilute aqueous ammonia. The solution was evaporated under reduced pressure and excess water removed by the addition and evaporation of ethanol from the residue. The residue solidified in ethyl acetate and crystallisation from ethanol-ethyl acetate gave 1.2 g. (54%) of the carbamoyl quinolizinium salt (108), m.p. 292-4°.

$C_{12}H_{13}N_2OBr$ requires: C, 52.16; H, 4.66; N, 9.96%

Found: C, 52.3; H, 4.61; N, 9.7%

$\nu_{max.}$ (Nujol) 1690 cm.$^{-1}$ (amide CO)

Attempted Synthesis of 1-Amino-7,8-dimethylquinolizinium Picrate, (109, X = Picrate).

To a stirred solution of 1.9 g. of 1-carbamoyl-7,8-dimethyl-quinolizinium bromide (108) and 1.7 g. of sodium hydroxide in 14 ml. of

water was added 0.5 ml. of bromine. When complete solution was attained, the mixture was heated at 70° for 30 minutes. The solution was cooled and aqueous sodium picrate added. The resulting precipitate would not crystallise from alcohol.

3-Nitro-2,6-lutidine,(110).

Prepared by the nitration of 2,6-lutidine by the method of Brown and Neil.[55]

6-Carboxy-3-nitro-2-picoline,(111).

Prepared by the oxidation of 3-nitro-2,6-lutidine also by the method of Brown and Neil.[55]

2,3-Dimethyl-1-carbethoxymethylpyridinium Picrate,(113, X = Picrate).

A solution of 5 g. of 2,3-lutidine and 7 g. of ethyl bromoacetate in 40 ml. of ethanol was boiled under reflux for 5 hr. The solvent was evaporated under reduced pressure and the residue solidified in ethyl acetate. Crystallisation from ethanol-ethyl acetate gave 11.8 g. (90%) of the quaternary salt (113). For analysis, the picrate was prepared by the addition of aqueous sodium picrate to an aqueous solution of the quaternary salt (113) and crystallised from ethanol as yellow prisms, m.p. 107-107.5°.

$C_{17}H_{18}N_4O_9$ requires: C, 48.34; H, 4.30; N, 13.27%

Found: C, 48.54; H, 4.41; N, 13.60%

$\nu_{max.}$ (Nujol) 1740 cm.$^{-1}$ (ester CO).

1,7,8-Trimethylquinolizinium Picrate, (114, X = Picrate).

A solution of 2 g. of 2,3-dimethyl-1-carbethoxymethylpyridinium bromide (113) with 2 g. of diacetyl and 1 g. of di-n-butylamine in 30 ml. of ethanol was boiled for 1 hour. The solvent was removed under reduced pressure and the residue solidified in ether. Crystallisation from ethanol-ether gave 1.1 g. (61%) of the quinolizinium salt (114). The picrate was prepared for analysis by the addition of aqueous sodium picrate to an aqueous solution of the trimethyl quinolizinium salt (114) and crystallised from ethanol as yellow needles, m.p. 184°.

$C_{18}H_{16}N_4O_7$ requires: C, 54.00; H, 4.03; N, 14.00%

Found: C, 54.03; H, 4.27; N, 14.28%

1-Carbethoxy-2-hydroxyindolizine, (116).

(a) 1,2-Dicarbethoxymethylpyridinium bromide (115) was prepared by treatment of 3.5 g. of ethyl pyridylacetate in 30 ml. of sulpholane with 6 g. of ethyl bromoacetate. The mixture was kept at 35° for 3 days. The addition of ethyl acetate to the reaction mixture gave a white crystalline solid, in 3.9 g. yield (56%). $\nu_{max.}$ (Nujol) 1750, 1740 $cm.^{-1}$

(b) 1.5 g. of 1,2-dicarbethoxymethylpyridinium bromide (115) was boiled in 20 ml. of ethanol with 0.8 g. of di-n-butylamine for 40 minutes. The solution was evaporated under reduced pressure and the residue taken up in hot carbon tetrachloride. The insoluble material was di-n-butylamine hydrobromide. Evaporation of the carbon tetrachloride solution to a small volume gave 0.6 g. (75%) of 1-carbethoxy-2-hydroxyindolizine (116), m.p. 129-130° (lit.[56] m.p. 131-132°).

4-Nitro-2-picoline-N-oxide.

Prepared by the nitration of 2-picoline-N-oxide by the method of Ochiai.[57]

4-Amino-2-picoline,(117).

Prepared by the reduction of 4-nitro-2-picoline-N-oxide by the method of Den Hertog, Colder and Combe.[58]

4-Acetamido-2-picoline,(118).

A solution of 8 g. of 4-amino-2-picoline in 60 ml. of acetic anhydride was boiled for 1 hour. The solution was cooled and made alkaline with aqueous sodium carbonate giving a white crystalline solid. Recrystallisation from carbon tetrachloride gave 8 g. (73%) of 4-acetamido-2-picoline (118) m.p. 110.5 - 111°.

$C_8H_{10}N_2O$ requires: C, 63.98; H, 18.65; N, 6.71%

Found: C, 64.0; H, 18.8; N, 6.55%

$\nu_{max.}$ (Nujol) 1690 cm.$^{-1}$ (acetamido CO)

4-Acetamido-2-methyl-1-carbethoxymethylpyridinium Bromide,(119).

A solution of 4.0 g. of 4-acetylamino-2-picoline and 5.5 g. of ethyl bromoacetate in 50 ml. of ethanol was boiled for 5 hours. The solvent was evaporated under reduced pressure and residue solidified in ethyl acetate. Crystallisation from ethanol gave 7.2 g. (74%) of the quaternary salt (119) with a molecule of ethanol of recrystallisation, m.p. 183-183.5°.

$C_{12}H_{17}N_2O_3Br.C_2H_5OH$ requires: C, 46.3; H, 6.38; N, 7.7%

Found: C, 46.3; H, 6.16; N, 8.1%

$\nu_{max.}$ (Nujol) 1745 cm.$^{-1}$ (ester CO) 1725 cm.$^{-1}$ (acetamido CO).

The picrate was prepared by the addition of aqueous sodium picrate to an aqueous solution of the quaternary salt (119) and crystallised from ethanol as yellow needles, m.p. 165-6°.

$C_{18}H_{19}N_5O_{10}$ requires: C, 46.45; H, 4.12; N, 15.05%

Found: C, 46.7; H, 4.01; N, 14.6%

2-Acetamido-7,8-dimethylquinolizinium Bromide, (120).

A solution of 2.0 g. of 4-acetamido-2-methyl-1-carbethoxymethylpyridinium bromide (119) in 30 ml. of ethanol was boiled for 1 hour with 1.0 gm. of diacetyl and 1.0 g. of di-n-butylamine. The solution was evaporated under reduced pressure and the residue crystallised from ethyl acetate. Recrystallisation from ethanol-ethyl acetate gave 1.4 g. (73%) of the acetamidoquinolizinium salt (120) with water of crystallisation, m.p. >320°.

$2CH_{13}H_{15}N_2OBr.H_2O$ requires: C, 51.34; H, 5.30; N, 10.00%

Found: C, 51.5; H, 5.12; N, 10.4%

$\nu_{max.}$ (Nujol) 1695 cm.$^{-1}$ (acetamido CO).

The picrate precipitated from an aqueous solution of the acetamido--quinolizinium salt (120) with aqueous sodium picrate and recrystallised from ethanol as yellow needles, m.p. 212-4°.

$C_{19}H_{17}N_5O_8$ requires: C, 51.47; H, 3.86; N, 15.80%

Found: C, 51.1; H, 3.67; N, 15.9%

2-Amino-7,8-dimethylquinolizinium Picrate, (121, X = Picrate).

A solution of 3.0 g. of 2-acetamido-7,8-dimethylquinolizinium bromide (120) in 50 ml. of 48% hydrobromic acid was boiled for 1 hour. The acid was removed under reduced pressure; ethanol was added to

the residue and also removed under reduced pressure. The residue solidified on the addition of ethyl acetate, and crystallisation from ethanol-ethyl acetate gave 2.3 g. (92%) of the aminoquinolizinium bromide (121, X = Br). The picrate was prepared for analysis by the addition of aqueous sodium picrate to a solution of the amine (121) in water and crystallised from ethanol as yellow-brown needles, m.p. 210--211°.

$C_{17}H_{15}N_5O_7$ requires: C, 50.87, H, 3.77, N, 17.45%

Found: C, 50.6, H, 3.63, N, 17.8%

2-Acetamido-7,8-diphenylquinolizinium Bromide,(122).

A solution of 4.4g. of the 4-acetamido-2-methylpyridinium bromide (119) in 30 ml. of ethanol was boiled under reflux for 1 hr. with 3.0 g. of benzil and 2 g. of di-n-butylamine. The solution was evaporated to dryness under reduced pressure and the residue dissolved in the minimum amount of hot water. On cooling the aqueous solution, the acetamido-diphenylquinolizinium salt (122) crystallised and was recrystallised from ethanol in 4.0 g. (66%) yield. Although the compound gave incorrect analyses, acid hydrolysis gave 2-amino-7,8--diphenylquinolizinium bromide (123, X = Br) which was analysed as the perchlorate (123, X = ClO_4).

The filtrate of the cold aqueous solution of the residue from the reaction was evaporated under reduced pressure; ethanol was added and also removed under reduced pressure. The remaining solid crystallised from ethyl acetate and was shown to be 4-amino-2-methyl-1--carbethoxymethylpyridinium bromide (124) identical with that obtained

by the procedure described below.

4-Amino-1-carbethoxypyridinium Bromide,(124).

A solution of 1.7 g. of 4-acetamido-2-methyl-1-carbethoxypyridinium bromide (119) in 30 ml. of ethanol was boiled under reflux for 2 hours with 1.0 g. of di-n-butylamine. The solvent was removed under reduced pressure and the residue solidified in ethyl acetate. The solid crystallised from ethanol giving 1.4 g. (93%) of the amino-pyridinium salt (124) as the dihydrate, m.p. 201-202°.

$C_{10}H_{15}N_2O_2Br.2H_2O$ requires: C, 38.59, H, 4.86, N, 9.00%

Found: C, 38.7, H, 4.89, N, 9.08%

$\nu_{max.}$ (Nujol) 3500, 3330, 3130 (NH), 1750 (ester CO), 1650 (strong) $cm.^{-1}$.

The picrate precipitated from an aqueous solution of the amine (124) and sodium picrate and crystallised from ethanol as yellow prisms, m.p. 152°.

$C_{16}H_{17}N_5O_9$ requires: C, 45.39; H, 4.05; N, 16.54%

Found: C, 45.3; H, 4.12; N, 16.1%

2-Amino-7,8-diphenylquinolizinium Perchlorate,(123, X = ClO_4).

A solution of 1.5 g. of 2-acetamido-7,8-diphenylquinolizinium bromide (122) in 30 ml. of 48% hydrobromic acid was boiled under reflux for 1 hour. The acid was boiled off under reduced pressure and excess water removed by the evaporation of ethanol from the residue. The residue solidified in ethyl acetate. Crystallisation from ethanol-ethyl acetate gave 1.1 g. (85%) of the amino-quinolizinium bromide (123, X = Br). The perchlorate (123, X = ClO_4) was prepared for analysis by the addition of acetone to a solution of the amine (123) in 65% perchloric

acid. Recrystallisation from ethanol gave a melting point of 230-231.5°.

$C_{21}H_{17}N_2O_4Cl$ requires: C, 63.54, H, 4.32, N, 7.06%

Found: C, 63.4, H, 4.24, N, 7.12%

2-Acetamidomethylpyridine,(125).

This was prepared by the acetylation of 2-picolylamine by the method of Bower and Ramage.[59]

2-Acetamidomethyl-1-carbethoxymethylpyridinium Bromide,(126).

A solution of 9.0 g. of 2-acetamidomethylpyridine (125) and 11.5 g. of ethyl bromoacetate in 20 ml. of sulpholane was kept at 35° for 3 days. Ethyl acetate was added to the solution until a viscous oil separated and the solution was decanted. Although it was not possible to prepare a crystalline picrate from the oil, the nuclear magnetic resonance spectrum of a dried sample of the oil in deuterium oxide confirmed its structure. The spectrum showed three singlets at 4.2, 5.1 and 7.8τ corresponding to two methylene groups and a methyl group, respectively. A carbethoxy group was present with a methyl-triplet centred at 8.7τ and a methylene-quartet at 5.6τ . Multiplets in the aromatic region integrated in the ratio of four protons.

1-Acetamido-2,3-dimethylquinolizinium Bromide,(128, R = CH_3).

50 ml. of an ethanolic solution of 2-acetamidomethyl-1-carbethoxymethylpyridinium bromide (126) from 9.0 g. of 2-acetamidomethylpyridine (125), was boiled under reflux with 4.0 g. of diacetyl and 2.3 g. of di-n-butylamine for 1 hour. The solvent was boiled off under

reduced pressure and the residue solidified in ethyl acetate. Crystallisation from ethanol gave 9.8 g. of the quinolizinium salt (128, R = CH_3), m.p. 286-288°, as purple prisms. The yield, based on 2-acetamidomethylpyridine as starting material, was 54%.

$C_{13}H_{15}N_2OBr$ requires: C, 52.89, H, 5.12, N, 9.49%

Found: C, 52.71, H, 5.51, N, 9.42%

$\nu_{max.}$ (Nujol) 1695 cm.$^{-1}$ (acetamide CO).

The picrate was prepared by the addition of aqueous sodium picrate to an aqueous solution of the quinolizinium salt (128, R = CH_3) and crystallised from ethanol as yellow needles, m.p. 221-2°.

$C_{19}H_{17}N_5O_8$ requires: C, 51.47, H, 3.86, N, 15.8%

Found: C, 51.34, H, 3.83, N, 15.4%

1-Acetamido-2,3-diethylquinolizinium Bromide, (128, R = Et).

A solution of 2-acetamidomethyl-1-carbethoxymethylpyridinium bromide (126) from 9.0 g. of 2-acetamidomethylpyridine (125) in 50 ml. of ethanol was boiled under reflux with 6.0 g. of dipropionyl and 2.3 g. of di-n-butylamine for 1 hour. The solution was boiled to dryness under reduced pressure and the residue solidified in ethyl acetate. Crystallisation from ethanol-ethyl acetate gave 7.8 g. (41%) of the quinolizinium salt (128, R = Et) as green prisms, m.p. 235°.

$C_{15}H_{19}N_2OBr$ requires: C, 55.75, H, 5.94, N, 8.67%

Found: C, 55.9, H, 5.94, N, 8.6%

$\nu_{max.}$ (Nujol) 1695 cm.$^{-1}$ (acetamido CO).

1-Amino-2,3-dimethylquinolizinium Bromide, (129, R = CH_3, X = Br).

A solution of 2.6 g. of 1-acetamido-2,3-dimethylquinolizinium bromide (128, R = CH_3) in 40 ml. of hydrobromic acid (48%) was boiled under reflux for 1 hour. The acid was removed under reduced pressure and excess water removed by the evaporation of ethanol from the residue. The residue solidified in ethyl acetate. Crystallisation from ethanol-ethyl acetate gave 1.9 g. (90%) of the aminoquinolizinium salt (129, R = CH_3), m.p. 296-298°.

$C_{11}H_{13}N_2Br$ requires: C, 52.15; H, 5.18; N, 11.07%

Found: C, 51.9; H, 5.26; N, 11.0%

The picrate was obtained from an aqueous solution of the amine (129, R = CH_3) and sodium picrate and was crystallised from ethanol as yellow needles, m.p. 207-8°.

$C_{17}H_{15}N_5O_7$ requires: C, 50.87; H, 3.77; N, 17.45%

Found: C, 51.3; H, 3.78; N, 17.41%

1-Amino-2,3-diethylquinolizinium Picrate, (129, R = Et, X = Picrate).

A solution of 1.8 g. of 1-acetamido-2,3-diethylquinolizinium bromide (128, R = Et) in 30 ml. of 48% hydrobromic acid was boiled under reflux for 1 hour. The solution was evaporated to dryness under reduced pressure and excess water removed by the evaporation of ethanol from the residue. The residue solidified in ethyl acetate and crystallisation from ethanol-ethyl acetate gave 1.4 g. (88%) of the quinolizinium salt (129, R = Et). The picrate was prepared for analysis by the addition of aqueous sodium picrate to an aqueous solution of the compound (129, R = Et) and crystallised from ethanol as yellow needles, m.p. 172°.

$C_{19}H_{19}N_5O_7$ requires: C, 53.14, H, 4.46, N, 16.31%

Found: C, 53.5, H, 4.27, N, 16.4%

N-Benzyl-pyridine-2-aldimine,(138).

A solution of 20.0 g. of 2-pyridine aldehyde in 200 ml. of benzene was boiled for 4 hours with 20.0 g. of benzylamine. The water formed during the reaction was removed with a Dean-Stark apparatus. The benzene was evaporated and the residue distilled giving 30.0 g. (82%) of the imine (138) as a pale-yellow liquid, b.p. 123-125°/0.2 mm Hg.

$C_{13}H_{12}N_2$ requires: C, 79.56; H, 6.16; N, 14.28%

Found: C, 79.5; H, 5.93; N, 14.0%

2-Benzylaminomethylpyridine,(139).

15.0 g. of the imine (138) were hydrogenated in 80 ml. of ethanol using 1.2 g. of 10% palladium-charcoal as the catalyst. After the uptake of 1 mole equivalent of hydrogen (3430 ml. at N.T.P.) the solution was filtered and the solvent evaporated under reduced pressure. The residue was distilled giving 14.0 g. (91%) of the secondary amine (139) b.p. 122-4°/0.15 mm Hg.

$C_{13}H_{14}N_2$ requires:C, 78.75; H, 7.12; N, 14.13%

Found:C, 78.5; H, 6.74; N, 13.8%

2-N-Benzylacetamidomethylpyridine,(140).

A solution of 9.0 g. of 2-benzylaminomethylpyridine (139) in 80 ml. of acetic anhydride was boiled under reflux for 1 hour. The acetic anhydride was removed under reduced pressure (water pump) and the residue distilled giving 10.0 g. (91%) of the acetyl compound (140)

as a viscous, yellow oil, b.p. 152-154°/0.1 mm Hg.

$C_{15}H_{16}N_2O$ requires: C, 74.97, H, 6.71, N, 11.66%

Found: C, 75.34, H, 7.09, N, 11.82%

$\nu_{max.}$ (Nujol) 1650 cm.$^{-1}$ (broad)

2-N-Benzylacetamidomethyl-1-carbethoxymethylpyridinium Bromide, (141)

A solution of 10.0 g. of 2-benzylacetamidomethylpyridine (140) and 8.0 g. of ethyl bromoacetate in 100 ml. of sulpholane was kept at 35° for 3 days. Ethyl acetate was added to the solution until a viscous oil separated. The solution was then decanted. It was not possible to isolate a crystalline picrate from an aqueous solution of the oil with aqueous sodium picrate.

1-N-Benzylacetamido-2,3-dimethyl-4-carbethoxyquinolizinium Bromide, (143).

The pyridinium salt (141) obtained as an oil from 10.0 g. of 2-benzylacetamidomethylpyridine (140) was dissolved in 50 ml. of ethanol and the solution boiled under reflux for 1 hour with 5.0 g. of diacetyl and 2.5 g. of di-n-butylamine. The solution was boiled to dryness under reduced pressure and the residue solidified in ether. Crystallisation from ethanol-ethyl acetate gave 4.0 g. (21%) of the quinolizinium salt (143), m.p. 179°.

$C_{23}H_{25}N_2O_3Br$ requires: C, 60.40, H, 5.51, N, 6.13%

Found: C, 60.7, H, 5.55, N, 6.1%

$\nu_{max.}$ (Nujol) 1740 cm.$^{-1}$ (ester CO) 1670 cm.$^{-1}$ (acetamido CO).

The picrate was prepared by adding a saturated solution of aqueous sodium picrate to an aqueous solution of the bromide (143). Crystallisation from ethanol gave the picrate as yellow needles, m.p. 172-3°.

$C_{29}H_{27}N_5O_{10}$ requires: C, 57.52, H, 4.49, N, 11.57%

Found: C, 57.9, H, 4.34, N, 11.2%

1-N-Benzylacetamido-2,3-dimethyl-4-carbethoxyquinolizidine Hydrobromide, (145).

1.0 g. of 1-N-benzylacetamido-2,3-dimethyl-4-carbethoxy-quinolizinium bromide (143) was hydrogenated in 20 ml. of 95% ethanol using 0.2 g. of platinum oxide as the catalyst. After the absorption of 8 mole equivalents of hydrogen (420 ml. at N.T.P.), the solution was filtered and boiled to dryness under reduced pressure. The residue crystallised from acetone at -5°. Recrystallisation from acetone gave 0.9 g. (90%) of the quinolizidine hydrobromide (145), m.p. 162-163°.

$C_{23}H_{35}N_2O_3Br$ requires: C, 59.09, H, 7.54, N, 5.99%

Found: C, 59.2, H, 7.10, N, 6.0%

$\nu_{max.}$ (Nujol) 1750 cm.$^{-1}$ (ester CO) 1655 cm.$^{-1}$ (acetamido CO)

1-N-Benzylacetamido-2,3-dimethylquinolizinium Bromide, (142).

A solution of 1.0 g. of 1-benzylacetamido-2,3-dimethyl-4--carbethoxyquinolizinium bromide (143) in 50 ml. of acetic anhydride was boiled under reflux for 1 hour. The solution was boiled to dryness under reduced pressure and the residue solidified in acetone. Recrystallisation from ethanol-ethyl acetate gave 0.7 g. (87%) of the compound (142).

$C_{20}H_{21}N_2OBr$ requires: C, 62.34, H, 5.48, N, 7.27%

Found: C, 62.5, H, 5.40, N, 7.4%

$\nu_{max.}$ (Nujol) 1675 cm.$^{-1}$ (acetamido CO).

1-Diacetylamino-2,3-dimethylquinolizinium Bromide,(149).

0.6 g. of 1-acetamido-2,3-dimethylquinolizinium bromide (146) was added to 60 ml. of acetic anhydride and the solution boiled under reflux for 1 hour. The solution was evaporated to dryness under reduced pressure and the residue crystallised from ethyl acetate. Recrystallisation from ethanol gave 0.6 g. (100%) of the diacetyl compound (149) as pink prisms, m.p. 280°.

$C_{15}H_{17}N_2O_2Br$ requires: C, 53.44; H, 5.08; N, 8.31%

Found: C, 53.25; H, 5.16; N, 8.44%

$\nu_{max.}$ (Nujol) 1720 cm.$^{-1}$, 1710 cm.$^{-1}$ (CO).

1-Acetamido-2-carboxy-3-methylquinolizinium Bromide,(151), and 1-Amino--2-formyl-3-methylquinolizinium Bromide,(153).

A stirred solution of 2.0 g. of 1-acetamido-2,3-dimethylquinolizinium bromide (146) in 200 ml. of pyridine was boiled under reflux. n-Butanol was added to the solution until all the solid had dissolved. The solution was then cooled to approximately 90° and 1.6 g. of selenium dioxide added over a period of 5 minutes. The mixture was then boiled for 20 minutes, during which time a crude solid came out of solution. The solid was collected by filtration of the cooled solution and was recrystallised from ethanol containing a few drops of hydrobromic acid. The product was the carboxy quinolizinium salt (151) obtained in 0.8 g. (35%) yield, m.p. 227-8°.

$C_{13}H_{13}N_2O_3Br$ requires: C, 48.00; H, 4.03; N, 8.62%

Found: C, 48.1; H, 3.89; N, 8.4%

$\nu_{max.}$ (Nujol) 1720 cm.$^{-1}$ (acid CO) 1700 cm.$^{-1}$ (acetamido CO).

The filtrate of the reaction mixture was concentrated under reduced pressure to a volume of approximately 50 ml. The solution was filtered and evaporated to dryness. The residue was triturated with acetone giving 0.7 g. (33%) of crude 1-acetamido-2-formyl-3-methylquinolizinium bromide (152). This compound was identified by hydrolysis to the amino--analogue (153). A solution of 0.7 g. of the crude acetamido compound (152) in 20 ml. of 48% hydrobromic acid was boiled for 1 hour under reflux. The hot solution was filtered and cooled to 0° when a yellow solid crystallised. The solid recrystallised from water as yellow needles, m.p. >320°, and analysed as 1-amino-2-formyl-3-methylquinolizinium bromide (153). Yield = 0.4 g.

$C_{11}H_{11}N_2OBr$ requires: C, 49.46; H, 4.12; N, 10.49%

Found: C, 49.1; H, 4.08; N, 10.2%

$\nu_{max.}$ (Nujol) 1630 cm.$^{-1}$ 1580 cm.$^{-1}$

1-Acetamido-2,3-dimethyl-4-bromoquinolizinium Bromide, (155, X = Picrate).

A solution of 1.0 g. of 1-acetamido-2,3-dimethylquinolizinium bromide (146) and 4.0 g. of sodium acetate in 20 ml. of water was heated at 90°. To the stirred solution was added four equivalents of bromine. Heating was continued for 1 hour. The solution was then cooled and bromine again added, giving a viscous oil. The aqueous solution was decanted and the oil was dissolved in ethanol-acetone and crystallised from the concentrated solution. Recrystallisation from ethanol gave 0.3 g. (23%) of the bromo-compound (155). The infrared spectrum and melting point were identical to those of a specimen prepared by an alternative method. Details of this synthesis appear later (page

2,3-Dimethylquinolizinium Bromide, (42).

This compound was prepared by the cyclisation of 2-methyl--1-carbethoxymethylpyridinium bromide (41) by the procedure of Westphal, Jahn and Heffe.[26]

2-Carboxy-3-methylquinolizinium Bromide, (156).

A solution of 5.0 g. of 2,3-dimethylquinolizinium bromide (156) in 200 ml. of pyridine was boiled under reflux with stirring until complete solution was effected. The solution was cooled to approximately 90° and 5.0 g. of selenium dioxide added over a period of a few minutes. The solution was then boiled for 30 minutes. After cooling to room temperature, the solution was filtered and concentrated under reduced pressure to a volume of approximately 50 ml. The solution was again filtered and then evaporated to dryness under reduced pressure. The residue was triturated with acetone and crystallised from ethanol-ethyl acetate. Recrystallisation from the same mixture of solvents gave 3.8 g. (66%) of the acid (156), m.p. 236-237°.

$C_{11}H_{10}NO_2Br$ requires: C, 49.28; H, 3.75; N, 5.23%

Found: C, 49.2; H, 3.27; N, 5.0%

$\nu_{max.}$ (Nujol) 1715 cm.$^{-1}$ (acid CO).

The carboxylate (157) of the acid (156) was prepared by refluxing an ethanolic solution of the acid with Amberlite Resin (IRA 400, OH). The solution was evaporated to dryness and the residue solidified in ethyl acetate. The carboxylate recrystallised from ethanol-ethyl acetate.

$\nu_{max.}$ (Nujol) 1620 cm.$^{-1}$ (carboxylate CO).

4-Methylquinolizinium Bromide, (159).

This quinolizinium salt was obtained by aromatising 1-oxo-4--methyl-1,2,3,4-tetrahydroquinolizinium bromide (158) in boiling acetic anhydride. The synthesis was first reported by Glover and Jones.[16]

Quinolizinium Bromide, (30).

A solution of 1.0 g. of 4-methylquinolizinium bromide (159) in 60 ml. of pyridine was boiled under reflux with stirring until all the solid had dissolved. The solution was cooled to approximately 90° and 1.0 g. of selenium dioxide added over a period of a few minutes. The solution was boiled for 10 minutes and then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to a volume of about 30 ml. and again filtered. The filtrate was boiled to dryness under reduced pressure and the residue triturated with acetone. The resulting solid crystallised and recrystallised from ethanol-ethyl acetate in 0.6 g. (66%) yield. The infrared spectrum and melting point were the same as those of a sample obtained in a previous synthesis.[15]

3-Methylquinolizinium Bromide, (163).

A solution of 1.0 g. of 2-carboxy-3-methylquinolizinium bromide (156) with 0.5 g. of copper powder in 100 ml. of quinoline was stirred vigorously under reflux for 1 hour. Most of the quinoline was removed by steam distillation and the remainder by extraction from the aqueous reaction mixture with ether. The aqueous solution was boiled to dryness under reduced pressure and the residue solidified in ethyl acetate.

The solid was repeatedly recrystallised from ethanol-ethyl acetate giving a small yield of 3-methylquinolizinium bromide (163). The infrared spectrum and melting point were the same as those obtained from a specimen prepared by Glover and Jones.[16]

1-Acetamido-3-methyl-4-carbethoxyquinolizinium Bromide,(166).

The pyridinium salt 2-acetamidomethyl-1-carbethoxymethylpyridinium bromide (126) obtained as an oil from 9.8 g. of 2-acetamidomethylpyridine (125) was dissolved in 40 ml. of ethanol. The solution was boiled under reflux for 1 hour with 6.0 g. of an aqueous solution of 40% pyruvic aldehyde and 2.0 g. of di-n-butylamine. The solvent was evaporated under reduced pressure and excess water removed by the evaporation of ethanol from the residue. The residue solidified in ethyl acetate and recrystallisation from ethanol-ethyl acetate gave 9.6 g. of the quinolizinium salt (166), m.p. 175° with decomposition. The yield, based on 2-acetamidomethylpyridine as starting material, was 42%.

$C_{15}H_{17}N_2O_3Br$ requires: C, 51.01; H, 4.85; N, 7.93%

Found: C, 51.4; H, 4.95; N, 7.9%

$\nu_{max.}$ (Nujol) 1730 $cm.^{-1}$ (ester CO) 1700 $cm.^{-1}$ (acetamido CO).

1-Amino-3-methylquinolizinium Bromide,(167, X = Br).

A solution of 2.0 g. of 1-acetamido-3-methyl-4-carbethoxyquinolizinium bromide (166) in 20 ml. of 48% hydrobromic acid was boiled under reflux for 1 hour. The acid was removed under reduced pressure and excess water removed by the evaporation of ethanol from the residue. The crystalline residue was taken up in ethyl acetate, filtered and

recrystallised from ethanol-ethyl acetate giving 1.6 g. (89%) of the aminoquinolizinium salt (167), m.p. 290°.

$C_{10}H_{11}N_2Br$ requires: C,50.23 ; H,4.57 ; N,11.74%

Found: C,50.01; H,4.37 ; N,11.51%

The picrate was obtained by the addition of saturated aqueous sodium picrate to an aqueous solution of the bromide (167) and recrystallised from ethanol as golden prisms, m.p. 203-204°.

$C_{16}H_{13}N_5O_7$ requires: C, 49.62; H, 3.38; N, 18.08%

Found: C, 49.6; H, 3.33; N, 18.2%

1-Diacetylamino-3-methylquinolizinium Bromide, (168).

A solution of 0.8 g. of 1-acetamido-3-methyl-4-carbethoxyquinolizinium bromide (166) in 30 ml. of acetic anhydride was boiled under reflux for 1 hour. The solution was concentrated to dryness under reduced pressure and the residue solidified in ethyl acetate. Recrystallisation from ethanol gave 0.7 g. (77%) of the diacetylamino compound (168), m.p. 230°.

$C_{14}H_{15}N_2O_2Br$ requires: C, 52.04; H, 4.68; N, 8.69%

Found: C, 51.8; H, 4.63; N, 8.7%

$\nu_{max.}$ (Nujol) 1725 cm.$^{-1}$ 1710 cm.$^{-1}$

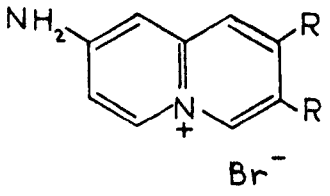
PROPERTIES OF 1- AND 2-AMINOQUINOLIZINIUM SALTS.

Discussion.

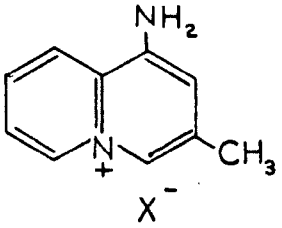
(a) Bromination.

The literature contains a number of references to the bromination of quinolizinium compounds. Benzo(b)quinolizinium bromide has been shown to undergo addition of bromine in ring C by reaction with liquid bromine at room temperature[68]. The substitution of bromine has been shown to occur with simpler quinolizinium compounds. Fozard and Jones[30,31,35] brominated 1-, 2- and 3-hydroxyquinolizinium bromides and obtained 1-hydroxy-2-bromo, 1-bromo-2-hydroxy and 3-hydroxy-4-bromoquinolizinium bromides, respectively. The reactions were performed by the addition of bromine to solutions of the hydroxy compounds in hydrobromic acid with subsequent heating. The bromination of 4-quinolizone is reported by Thyagarajan and Gopalakrishnan[69]. Using ethyl bromide as the brominating reagent and dimethyl sulphoxide as the solvent, substitution of bromine was shown to occur in position 3 of the quinolizone. Dibromination was found to occur in positions 1 and 3 when bromine in acetic acid was employed. As an extension to this work, the bromination of the aminoquinolizinium salts (169,R=CH_3,Ph), (167,X=Br) and (129,R=CH_3,Et,X=Br) has been investigated. Each of these amines gave monobromo substitution products in high yields. The reactions were performed by the addition of bromine to aqueous solutions of the amines at room

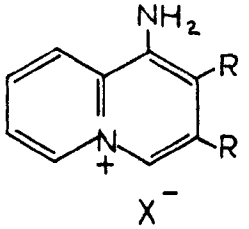
temperature. The products separated as tribromides and were converted to monobromides in solutions of alcohol mixed with acetone.



(169)



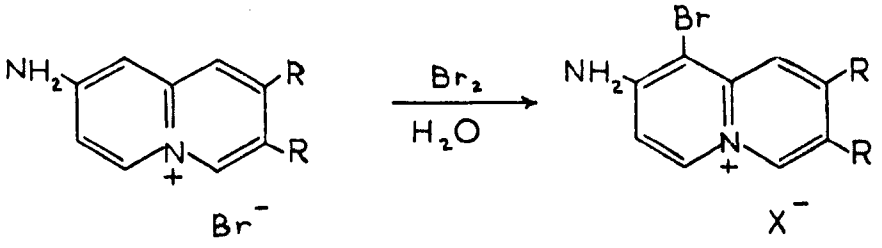
(167)



(129)

If the brominations of the 2-amino compounds (169,R=CH_3,Ph) and 2-hydroxyquinolizinium bromide were assumed to be analogous the 2-amino compounds would be expected to brominate in position 1. The 2-amino-7,8-dimethyl compound (169,R=CH_3) was brominated under the conditions described above and gave a monobromo derivative, formulated as 1-bromo-2-amino-7,8-dimethylquinolizinium bromide (170,R=CH_3, X=Br). The position of bromination was established by comparing the nuclear magnetic resonance spectra of the starting material and the product. The aromatic regions of these spectra are shown on page 124 . The spectrum of (169,R=CH_3) shows three broad singlets at 1.5, 2.1 and 2.3τ. These are assigned to the protons in positions 6, 9 and 1, respectively. The singlet at 2.3τ appears larger than the others as it is superimposed on the doublet due to the 3-proton, this being coupled to proton 4. The spectrum of the product (170,R=CH_3,X=Br) has peaks centred

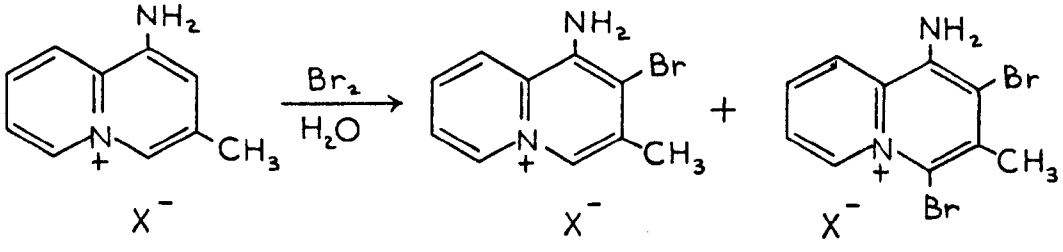
at 1.5τ and these are assumed to consist of a singlet, due to proton 6, superimposed on a doublet, due to proton 4. The singlet at 2.4τ may be assigned to either the 1- or 9-proton. However, since the amino group would be expected to make position 1 more susceptible to electrophilic attack than position 9, this singlet is assigned to proton 9 and the bromination product formulated as the 1-bromo derivative (170,R=CH_3,X=Br). The 2-amino-diphenyl compound (169,R=Ph) also gave a monobromo product, assumed to be 1-bromo-2-amino-7,8-diphenylquinolizinium bromide (170,R=Ph,X=Br).



(169) (170)

The 1-amino-3-methyl compound (167,X=Br) brominated not only in position 2, as would be expected by analogy with 1-hydroxyquinolizinium bromide, but also in position 4. The tribromide ($X=Br_3$) of 1-amino-2,4-dibromo-3-methylquinolizinium salt (172) was obtained by the addition of 2 molar equivalents of bromine to an aqueous solution of the amine (167,X=Br) at room temperature. The tribromide ($X=Br_3$) of 1-amino-2-bromo-3-methylquinolizinium salt (171) crystallised when the

aqueous solution was cooled to -5°.

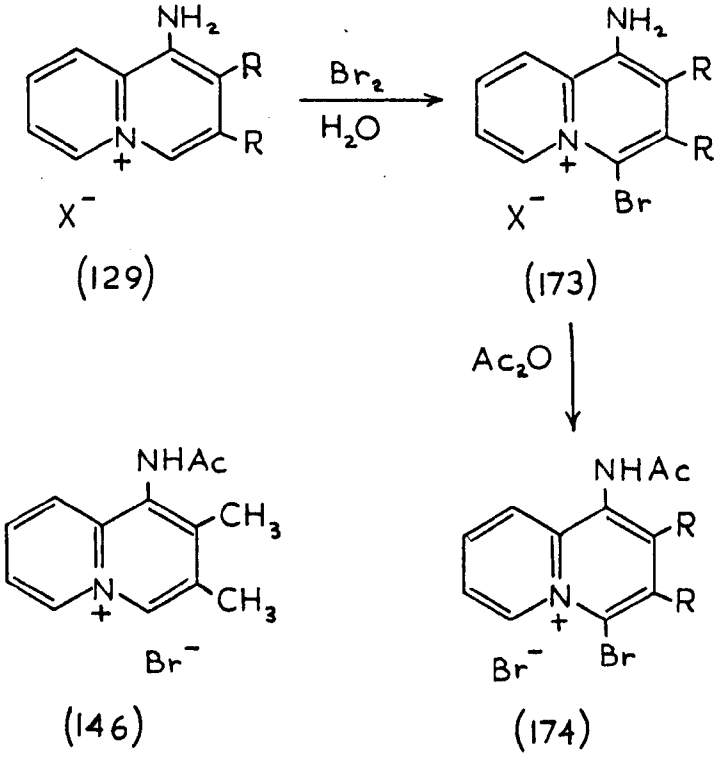


(167) (171) (172)

The nuclear magnetic resonance spectrum of the amine (167,X=Br), shown on page 123, has two peaks at 1.9 and 2.9τ which are assumed to be unresolved doublets due to the protons 4 and 2, respectively. The spectrum of the monobromo compound (171,X=Br) has no upfield peak corresponding to proton 2 in the starting material, indicating substitution in position 2. In the spectrum of the dibromo derivative (172,X=Br) the peaks corresponding to the 2- and 4-protons in the starting material are absent, indicating bromination in positions 2 and 4. The dibromo compound (172,X=Br) was also obtained by brominating the monobromo compound (171,X=Br). The spectra of (171,172,X=Br) are shown on page 125.

The apparent ease with which a 1-amino substituent promotes substitution in position 4 of the quinolizinium nucleus, was confirmed by studies on the bromination of the 1-amino-2,3-dimethyl compound (129,R=CH_3,X=Br). Under the usual conditions, the substitution reaction gave 1-amino-2,3-dimethyl-4-bromo-quinolizinium bromide (173,R=CH_3,X=Br). The position of

substitution was again confirmed by comparing the nuclear magnetic resonance spectra of the acetylated bromination product (174,R=CH_3) and the 1-acetamido-dimethyl compound (146). The spectra are shown on page 126. The amino group of the 4-bromo compound (173,R=CH_3,X=Br) was acetylated in boiling acetic anhydride. The spectrum of (146) shows a singlet at 1.0τ superimposed on a broadened doublet due to proton 6 (J_{6-7}=9 c.p.s., J_{6-8}~1 c.p.s.). This singlet is absent in the spectrum of (174) thus confirming position 4 as the site of bromination in the amine (129,R=CH_3,X=Br). The bromination of 1-amino-2,3-diethylquinolizinium bromide (129,R=Et,X=Br) gave 1-amino-2,3-diethyl-4-bromoquinolizinium bromide (173,R=Et,X=Br).

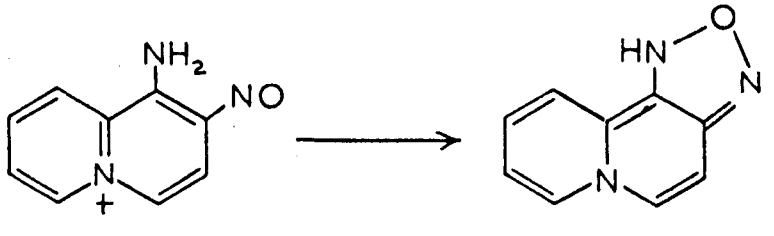


(129) (173) (146) (174)

The bromination of quinolizinium salts by the above procedure was successful only when attempted on the amino compounds (169), (167) and (129). The fact that an electron-donating group was required to activate the quinolizinium system to electrophilic attack was indicated by attempts to brominate non-activated quinolizinium salts by the same procedure. From the attempted brominations of 2,3-dimethylquinolizinium bromide and 1-acetamido-2,3-dimethylquinolizinium bromide (146), unchanged starting material was obtained in both cases. It was possible, however, to brominate the acetamido compound (146) in aqueous solution at 90°, giving a 23% yield of the 4-bromo derivative (174). (The reaction mixture was basified with sodium acetate as the aim of the reaction was to brominate the 2-methyl group, but the base must not be assumed to promote the nuclear bromination.). In this case the quinolizinium system appears to be sufficiently activated by the weakly electron-donating group, -NHAc, for bromination to occur, but when the bromination of 2,3-dimethylquinolizinium bromide was attempted under the same conditions, starting material was recovered.

(b) Nitrosation

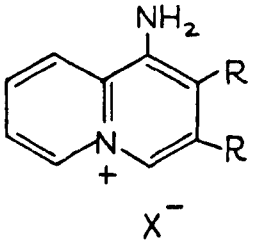
The studies of Collicut and Jones[39] on the properties of 1-aminoquinolizinium chloride includes the only reported reactions of an aminoquinolizinium salt with nitrous acid. Diazotisation of the amino group was achieved with amyl nitrite in a slightly acidic solution of ethanol. When diazotisation was attempted by the addition of aqueous sodium nitrite to a solution of the 1-amino compound in dilute hydrochloric acid, an insoluble compound formulated as the furazan (77) was obtained. The production of the furazan is taken as an indication of electrophilic substitution of the nitroso group in position 2 giving the intermediate nitroso compound (76). Cyclisation to the furazan (77) is then presumed to occur.



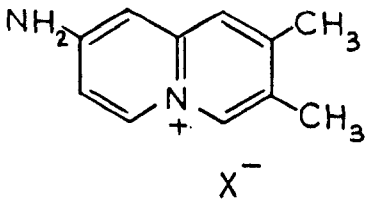
(76) (77)

As a further examination of the reactions of aminoquinolizinium compounds with nitrous acid in aqueous solution, the nitrosation of the compounds (129,R=CH_3,Et,X=Cl), (121,X=Cl) and (167,X=Cl) was investigated. Unless otherwise stated, solutions of each of these amines in 2N. hydrochloric acid at 0° were treated with

aqueous sodium nitrite.



(129)



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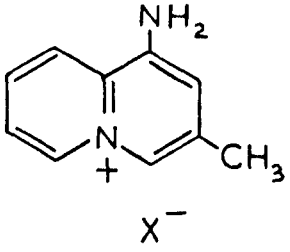
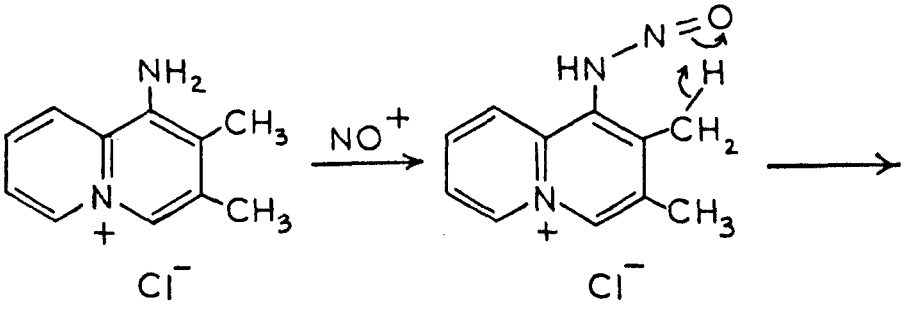
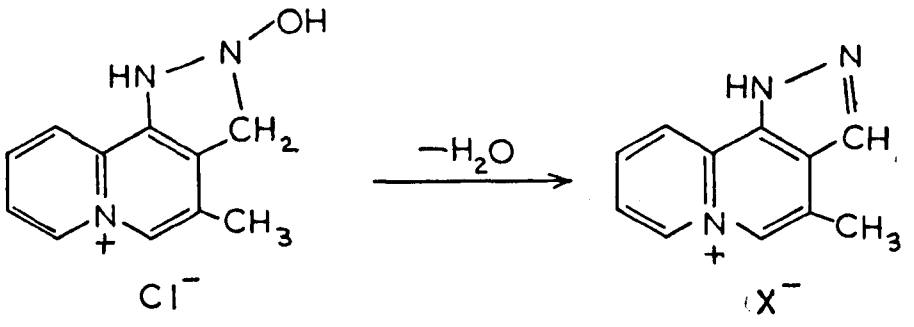


(167)

Initially, it was hoped to confirm the formation of the furazan (77) by synthesising a dimethyl analogue by the nitrosation of a 1-amino-7,8-disubstituted quinolizinium salt. It was possible to obtain a highly impure form of 1-amino-7,8-dimethylquinolizinium salt via the Westphal synthesis, and although the nitrosation of this compound was not attempted, the formation of a dimethyl analogue of (77) from this compound now seems doubtful as results indicate that a methyl group in the active 2- or 8-position of an aminoquinolizinium salt may take part in the reaction with nitrous acid. The supporting evidence was provided by the studies on the reaction of 1-amino-2,3-dimethylquinolizinium chloride (129, R=CH_3, X=Cl) with nitrous acid.

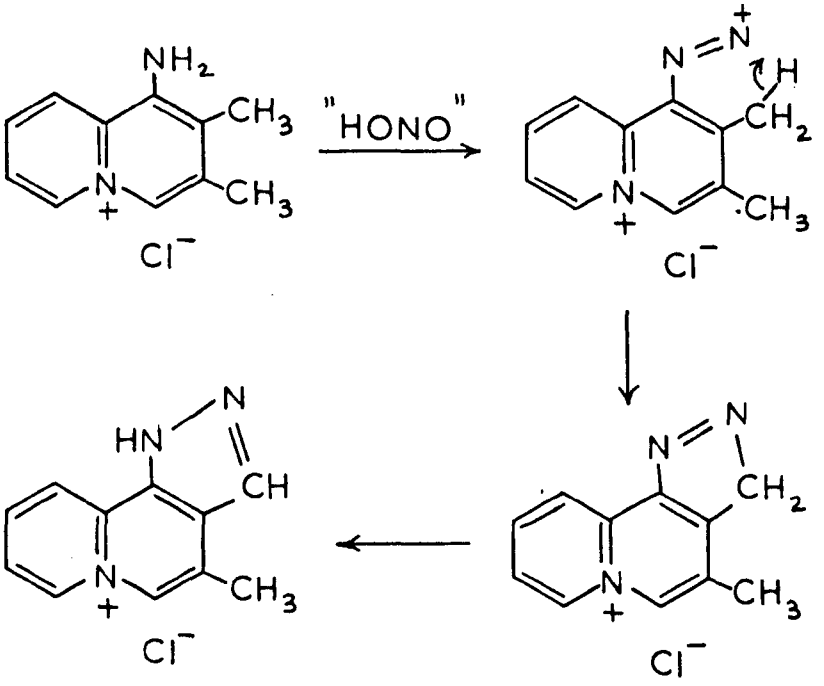
When the diazotisation of (129,R=CH_3,X=Cl) was attempted under the same conditions as employed by Collicut and Jones[39] for the formation of the furazan (77), an insoluble yellow product was obtained. This compound was virtually insoluble in all common organic solvents and was unstable in alkaline, neutral or slightly acidic solution, in each case a dark insoluble compound with a different infrared spectrum being produced. The yellow compound, however, was soluble in concentrated acid. Its nuclear magnetic resonance spectrum, determined in trifluoroacetic acid, showed a single peak at 7.0τ and multiple peaks in the aromatic region; the corresponding integrations were in the ratio 3:6.
In the spectrum of the starting material (129,R=CH_3,X=Cl), the two methyl groups appeared as singlets separated by 6 c.p.s.
The spectrum of the yellow product was therefore explicable in terms of a monomethyl compound of the type (175,X=Cl). The formation of the indazole ring could involve nitrosation of the amino group followed by cyclisation.





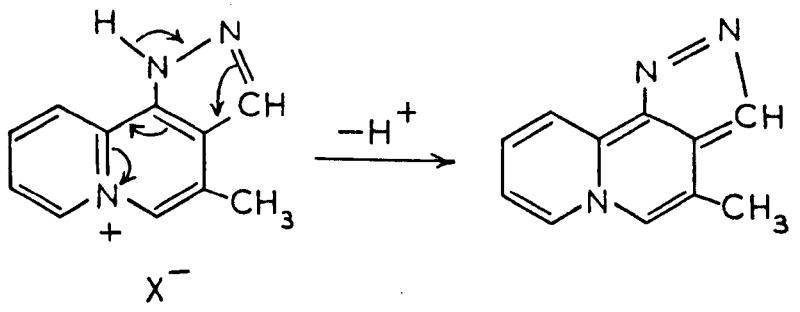
(175)

Alternatively, the reaction could proceed through the formation and subsequent cyclisation of a diazonium salt. The synthesis of indazoles via diazonium salts is discussed in chapter 3, volume 5 of Elderfield's "Heterocyclic Compounds".



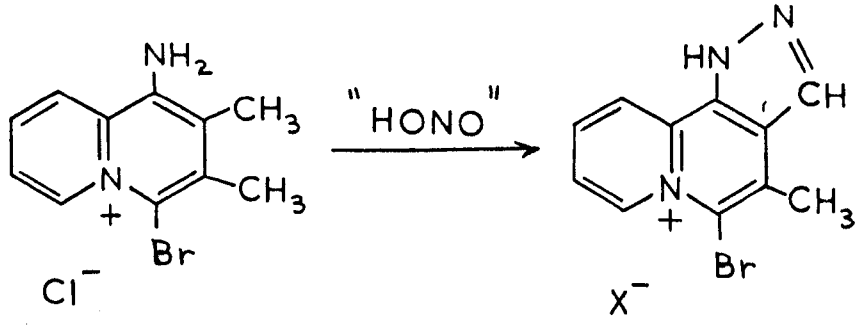
The instability of the tricyclic system (175), except under strongly acidic conditions, is attributed to a rearrangement to the neutral compound (176) by proton-loss from the nitrogen atom

in the five-membered ring.



(175)

A more stable system of the type (175) was obtained by the reaction of 1-amino-2,3-dimethyl-4-bromoquinolizinium chloride (177) with nitrous acid. The crude product (178,X=Cl) was obtained in 67% yield and was found to be stable in dilute acid. Its perchlorate (178,X=ClO_4) was soluble in alcohol and gave the correct analysis after crystallisation from ethanol containing a trace of perchloric acid.



(177) (178)

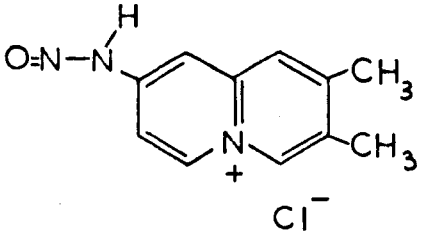
To obtain a more stable system of the type (175), an attempt was made to synthesise a tricyclic compound in which the

acidic hydrogen atom bonded to the nitrogen atom in the five-membered ring was replaced by a benzyl group. However, attempts to prepare the starting material, 1-N-benzylamino-2,3-dimethylquinolizinium bromide, for this reaction were unsuccessful due to the ease with which the benzyl group was removed from the intermediate 1-N-benzylacetamido-2,3-dimethyl-4-carbethoxyquinolizinium bromide (143) (see page 49). Further attempts to obtain a tricyclic compound with an alkyl substituent in the five-membered ring by nitrosation of 1-amino-2,3—diethylquinolizinium salt (129,R=Et) were unsuccessful. The reaction failed to give an insoluble product and it was not possible to isolate a picrate from the aqueous solution by the addition of aqueous sodium picrate.

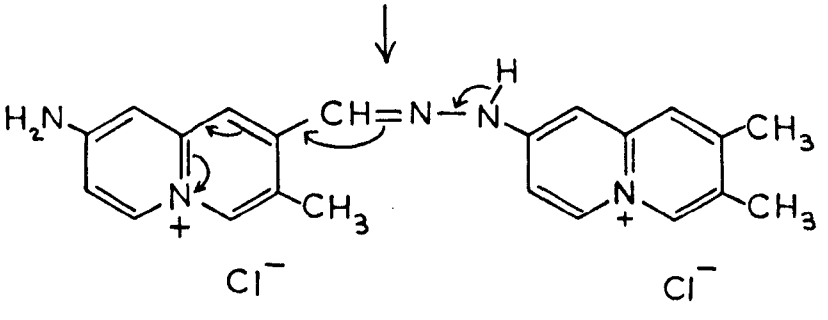
Syntheses of indazoles from compounds containing an active methyl group adjacent to an amino group are reported in the literature[70]. The synthesis of compound (178,X=Cl) from (177) is the first reported example in which the condensing methyl group is activated by a heterocyclic nucleus.

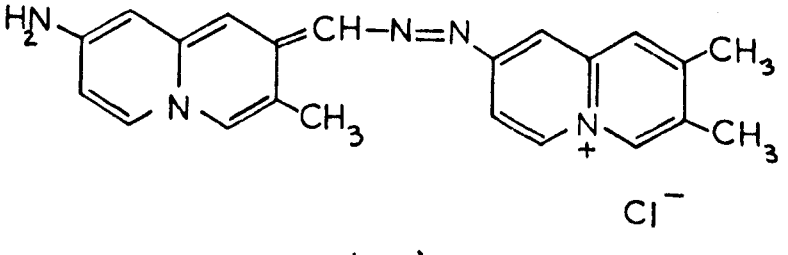
The reaction of 2-amino-7,8-dimethylquinolizinium chloride (121,X=Cl) with nitrous acid was expected to involve either C- or N-nitrosation. Substitution at carbon would be expected by analogy with the bromination of 2-amino-7,8-dimethylquinolizinium bromide. The resulting 1-nitroso compound (179) would not be expected to cyclise to a furazan since a completely aromatic, non-ionic structure cannot be drawn. N-nitrosation would give the N-nitroso compound (180). In view of the reactivity shown by the

2-methyl group in the cyclisation of (129,R=CH_3,X=Cl) to (175), the N-nitroso compound (180) would be expected to condense with a second molecule giving the dimer (181). By analogy with the coupling of N,N-dimethyl-p-nitrosoaniline with 2-methyl-quinolizinium salts,[12] the C-nitroso compound (179) would be expected to couple with a second molecule giving the dimer (182).

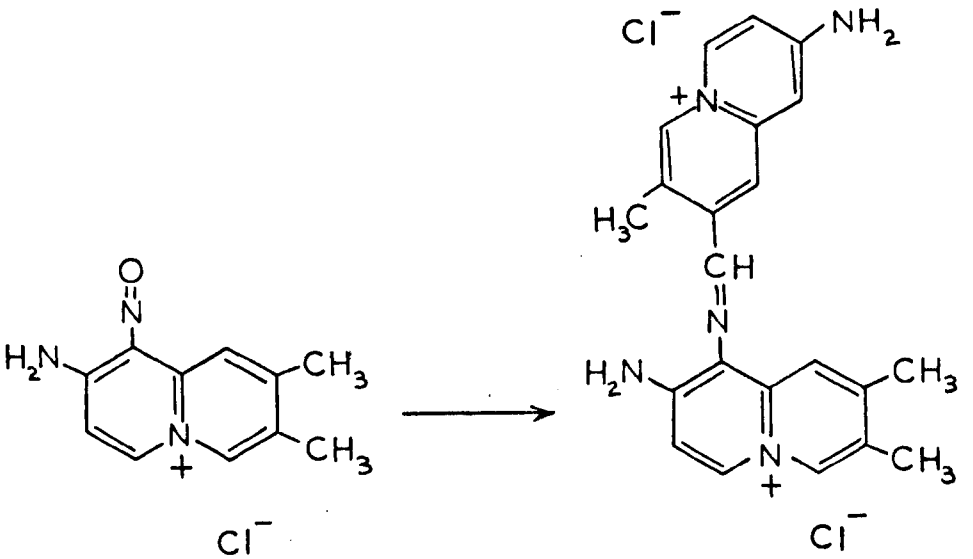


(180)





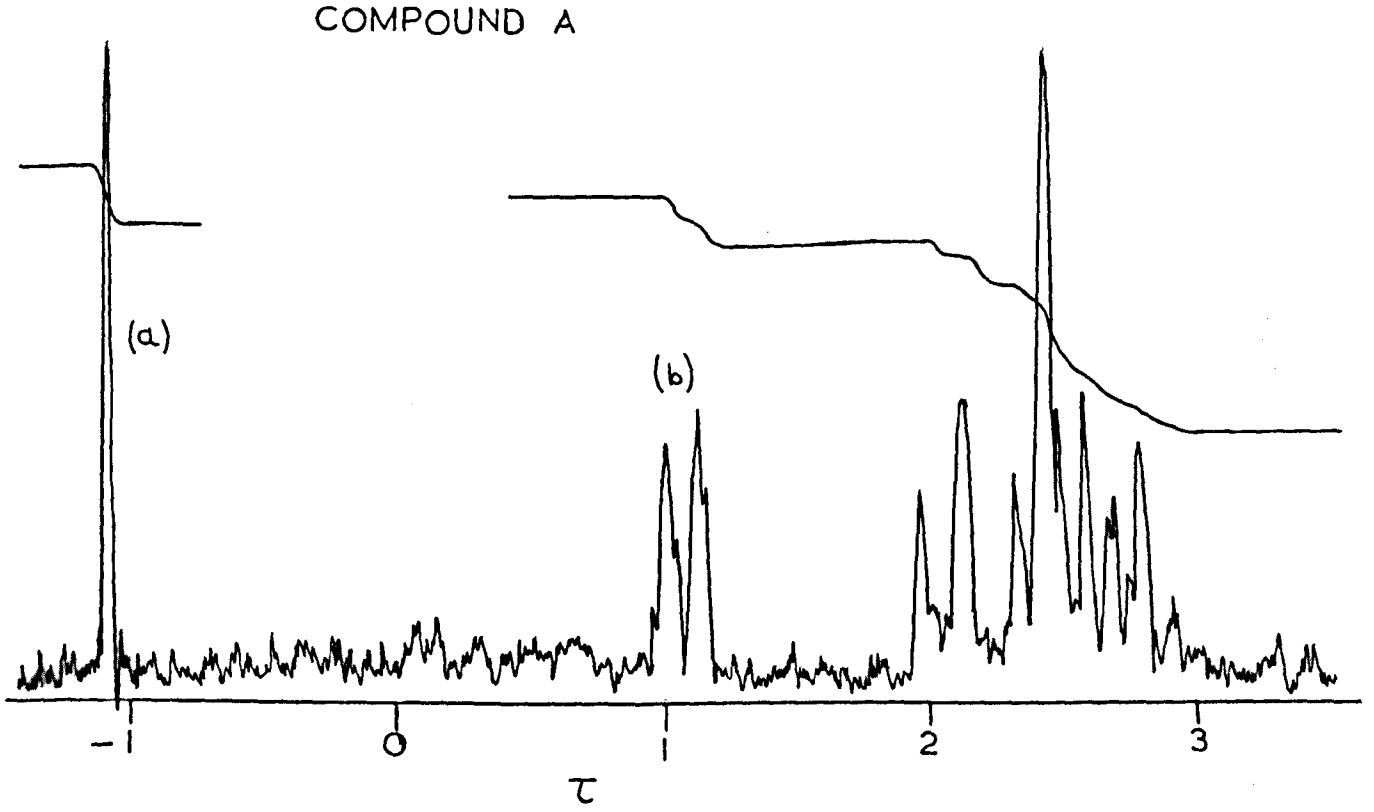
(181)

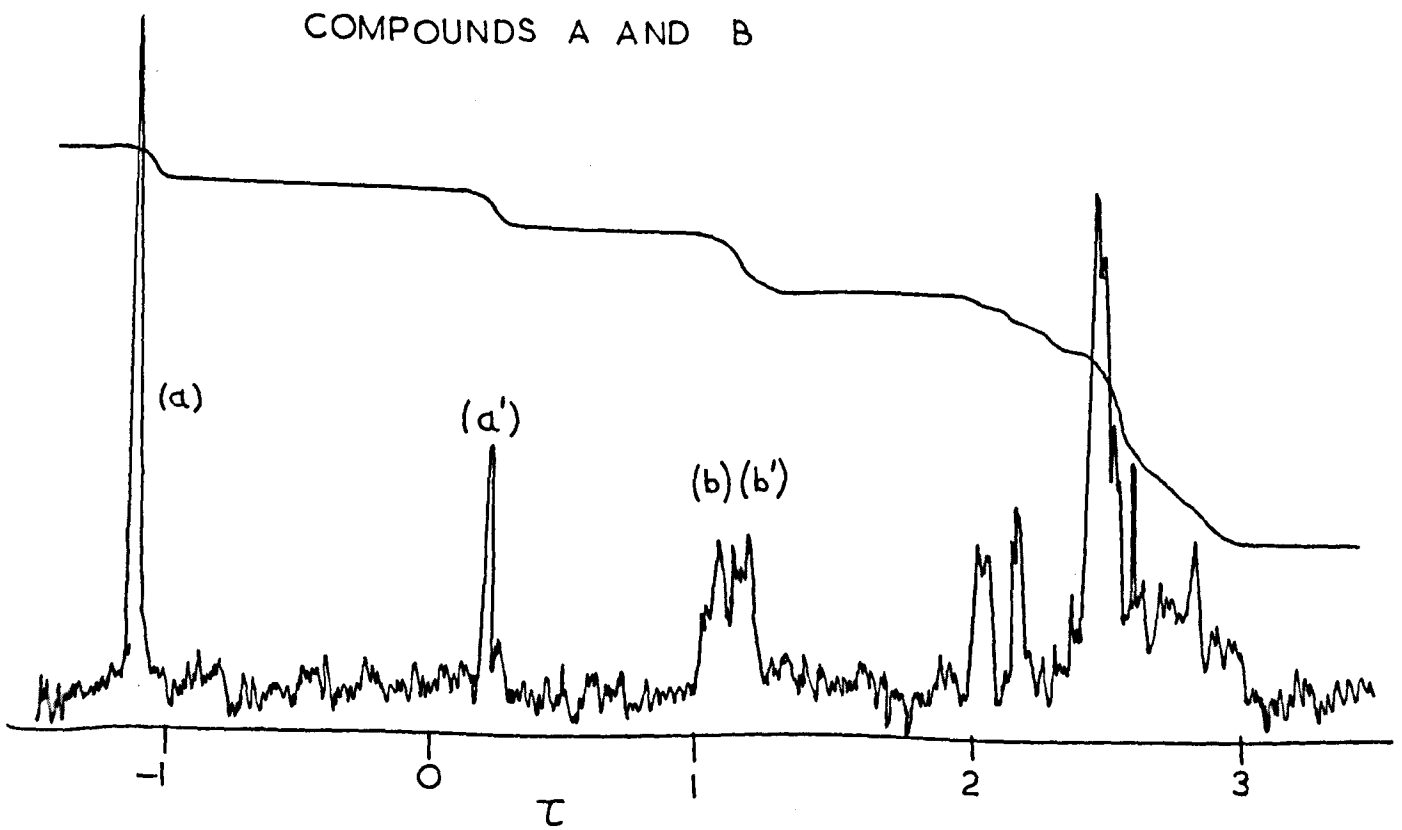


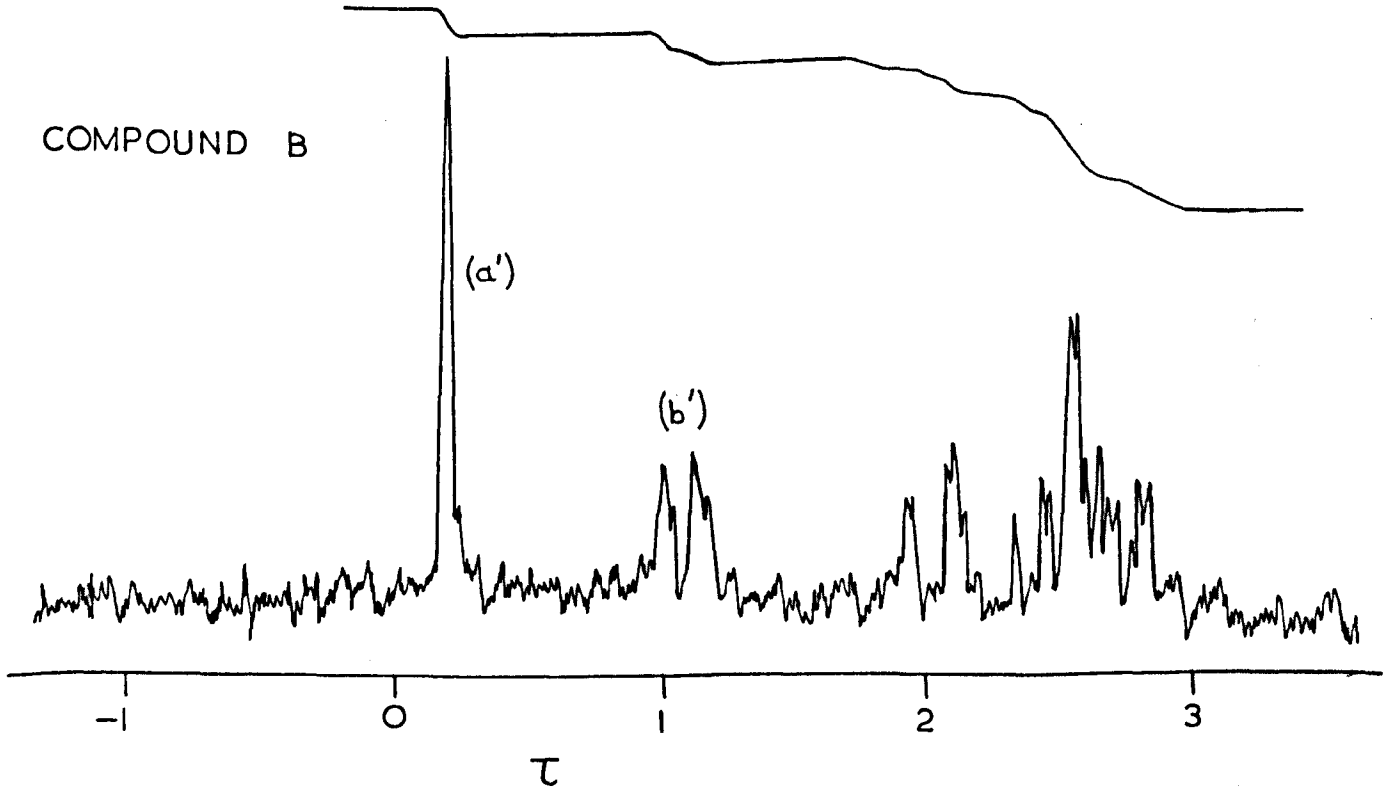
(179) (182)

From the reaction of the 1-amino compound (121,X=Cl) with nitrous acid, it was not possible to isolate a pure compound. However, the characteristic feature of the reaction was the production of a deep purple-coloured solution, indicative of the formation of a dye and explicable in terms of the production of a dimeric compound of the type (181) or (182). In order to distinguish between the two possibilities, the reaction of 1-bromo-2-amino-7,8-dimethyl-quinolizinium chloride with nitrous acid was investigated under the same conditions. Although no product was isolated from the reaction, the solution remained colourless and this is taken as an indication of preferential C-nitrosation in the case of the unsubstituted amine (121,X=Cl) leading to the dimer (181).

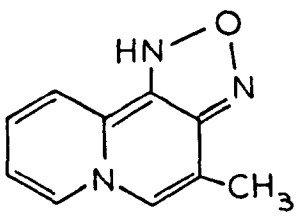
The nitrosation of 1-amino-2-methylquinolizinium chloride (167, X = Cl) was expected to produce a methyl-substituted furazan of the type (183). The reaction at 0° gave a poor yield of an insoluble compound, which will be referred to as compound (A), of empirical formula $C_{10}H_9N_3O$. The yield of (A) improved to 78% when the reaction was performed at room temperature. Compound (A) was shown to be susceptible to base under mild conditions. When treated with piperidine in ethanolic solution at room temperature for 1 hour, a compound (B) of the same empirical formula but different melting point and infrared spectrum was obtained. It was possible to record the conversion of (A) to (B) by determining the nuclear magnetic resonance spectrum of (A) in deuterochloroform (see next two pages). The spectrum was initially that of compound (A) and showed a sharp singlet (a) at -1.1τ , a broadened doublet (b) at 1.1τ and multiple peaks from 2 to 3τ . The spectrum of (B) developed over a period of 1 hour, after which time that of (A) had completely disappeared. The spectrum of (B) showed a sharp singlet (a') at 0.2τ , a broadened doublet (b') at 1.1τ and multiple peaks from 2 to 3τ . The conversion of (A) to (B) is attributed to the presence of base in the deuterochloroform since the change in the spectrum was observed in chloroform only when a trace of piperidine was added. The spectrum of the compound formulated as the furazan (77) showed a similar change in deuterochloroform. The spectrum differed from that of the methyl-substituted analogues in that each of the downfield singlets (a) and (a') were replaced by doublets. These downfield signals (a) and (a') are therefore attributed to the aromatic hydrogen atoms in


COMPOUND A
(a)
(b)
-1
0
1
2
3
τ


COMPOUNDS A AND B
(a)
(a')
(b) (b')
-1
0
1
2
3
τ

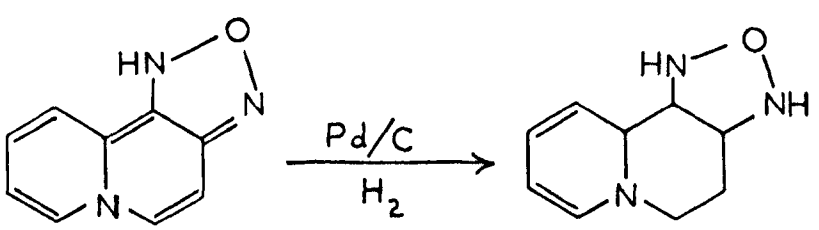

COMPOUND B
(a')
(b')
-1
0
1
2
3
τ

position 4 adjacent to the bridgehead nitrogen atoms. The mass spectra of the compounds (A) and (B) gave a molecular weight of 187 for both compounds, indicating that both were monomers. The conversion of (A) to (B) is therefore presumed to be a tautomeric change and one of the tautomers is presumed to have the structure (183).



(183)

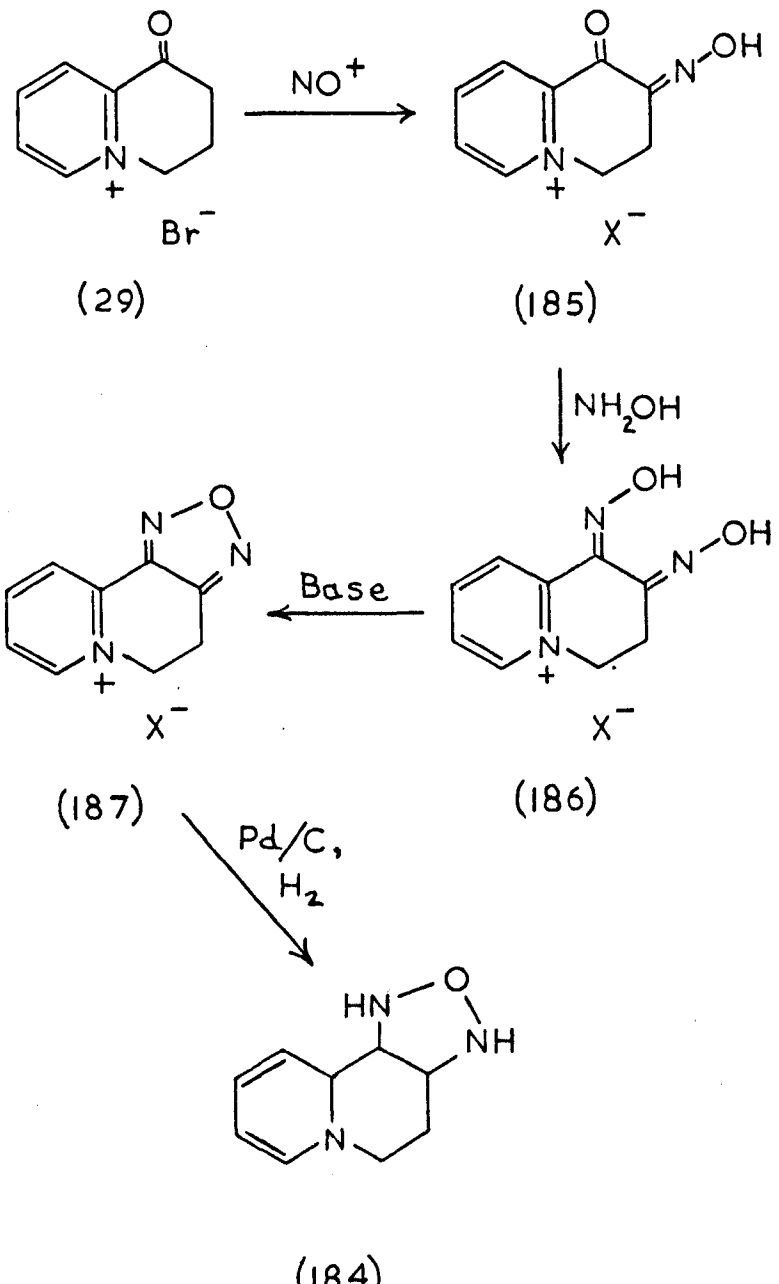
In order to confirm the structure of the furazan (77), attempts were made to synthesise a compound formulated by Collicut and Jones[39] as (184). The authors prepared this compound by catalytic reduction of the furazan (77).



(77) (184)

The alternative synthesis of (184) was to involve the catalytic reduction of the tricyclic system (187) which might be obtained by treatment of the glyoxime (186) with base. The proposed synthesis of the glyoxime (186)

was to involve nitrosation of 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (29) followed by treatment of the keto-oxime (185), so-formed, with hydroxylamine.



(29) (185) (186) (187) (184)

Although the keto-oxime (185, X = Cl) was obtained in 66% yield by nitrosation of the ketone (29) with amyl nitrite and dry hydrogen chloride, the attempted synthesis of the glyoxime (186) was unsuccessful. A solution of hydroxylamine was prepared from hydroxylamine hydrochloride and sodium acetate and was boiled with the keto-oxime (185, X = Cl) for 1 hour. When the solution was concentrated to a small volume, however, the keto-oxime (185, X = Cl) was recovered unchanged.

Experimental.

Bromination of the Amines (169,R=CH_3,Ph) and (129,R=CH_3,Et,X=Br).

An aqueous solution of each amine was stirred at room temperature and treated dropwise with bromine until a viscous oil separated. The oil solidified as a tribromide ($X=Br_3^-$) either on standing or by scratching the aqueous solution. The tribromide was filtered off, washed with water and dried in an evacuated dessicator. The monobromide ($X=Br^-$) crystallised by dissolving the tribromide in a mixture of ethanol and acetone and concentrating the solution to a small volume.

(a) 1-Bromo-2-amino-7,8-dimethylquinolizinium bromide, (170,R=CH_3,X=Br) was obtained in 90% yield from (169,R=CH_3). The picrate (170,R=CH_3,X=picrate) was obtained as a yellow crystalline solid by the addition of an aqueous solution of sodium picrate to an aqueous solution of the bromide and recrystallised from ethanol as golden needles, m.p. 245-6°.

$C_{17}H_{14}N_5O_7Br$ requires: C, 42.51; H, 2.94; N, 14.58%

Found: C, 42.6; H, 2.65; N, 14.5%

(b) 1-Bromo-2-amino-7,8-diphenylquinolizinium bromide, (170,R=Ph,X=Br) was obtained in 95% yield from (169,R=Ph) and crystallised from ethanol as yellow prisms, m.p. 320°.

$C_{21}H_{16}N_2Br_2$ requires: C, 55.27; H, 3.55; N, 6.14%

Found: C, 55.0; H, 3.65; N, 5.9%

(c) 1-Amino-2,3-dimethyl-4-bromoquinolizinium bromide, (173,R=CH_3,X=Br) was obtained in 90% yield from (129,R=CH_3,X=Br). The picrate (173,R=CH_3,X=picrate) was prepared by the addition of an aqueous solution of the bromide to an aqueous solution of sodium picrate and crystallised from ethanol as yellow needles, m.p. 226°.

$C_{17}H_{14}N_5O_7Br$ requires: C, 42.51; H, 2.94; N, 14.58%

Found: C, 42.8; H, 2.91; N, 14.6%

(d) 1-Amino-2,3-diethyl-4-bromoquinolizinium bromide, (173,R=Et,X=Br) was obtained in 90% yield from (129,R=Et,X=Br). The picrate precipitated from an aqueous mixture of sodium picrate and the bromide and crystallised from ethanol as golden leaflets, m.p. 218-220°.

$C_{19}H_{18}N_5O_7Br$ requires: C, 44.88; H, 3.57; N, 13.77%

Found: C, 45.2; H, 3.25; N, 13.9%

Bromination of 1-Amino-3-methylquinolizinium Bromide, (167,X=Br).

To a solution of 1.0 g. of the amine (167,X=Br) in 10 ml. of water at room temperature were added 2 molar equivalents of bromine. An oil separated from the solution and solidified on standing. The solid was filtered, dried

and dissolved in a mixture of ethanol and acetone. 1-Amino-2,4-dibromo-3-methylquinolizinium bromide (172,X=Br) crystallised from the concentrated solution and recrystallised from ethanol in 0.3 g. (17%) yield. The picrate (172,X=picrate) was obtained from an aqueous solution of the bromide and sodium picrate and crystallised from ethanol as yellow prisms, m.p. 229°.

$C_{16}H_{11}N_5O_7Br_2$ requires: C, 35.26; H, 2.03; N, 12.85%

Found: C, 35.7: H, 2.04; N, 12.5%

The filtrate of the reaction mixture was cooled to -5°. The solid which crystallised from the solution was filtered and dissolved in a mixture of ethanol and acetone. 1-Amino-2-bromo-3-methylquinolizinium bromide (171,X=Br) crystallised when the solution was concentrated to a small volume. Recrystallisation from ethanol gave 0.6 g. (52%) of the monobromo compound (171,X=Br). The picrate (171,X=picrate) was prepared from an aqueous solution of the bromide and sodium picrate and crystallised from ethanol as golden needles, m.p. 230-231°.

$C_{16}H_{12}N_5O_7Br$ requires: C, 41.21; H, 2.59; N, 15.02%

Found: C, 41.4; H, 2.69; N, 14.8%

1-Acetamido-2,3-dimethyl-4-bromoquinolizinium Bromide, (174,R=CH_3,X=Br).

A solution of 2.0 g. of 1-amino-2,3-dimethyl-4-

bromoquinolizinium bromide (173,R=CH_3,X=Br) in 60 ml. of acetic anhydride was boiled under reflux for 1 hour. The solution was evaporated to dryness under reduced pressure and the residue solidified by the addition of ethyl acetate. The solid recrystallised from ethanol-ethyl acetate giving 0.9 g. (58%) of the acetamido compound (174,R=CH_3,X=Br), m.p. 278°.

$C_{13}H_{14}N_2O_2Br_2$ requires: C, 40.02; H, 3.62; N, 7.18%

Found: C, 39.71; H, 3.52; N, 7.46%

Nitrosation of 1-Amino-2,3-dimethyl-4-bromoquinolizinium Chloride, (177).

The chloride (177) was obtained by passing a solution of 1-amino-2,3-dimethyl-4-bromoquinolizinium bromide, in 95% ethanol, down an ion-exchange column (Amberlite IR 400,Cl). The solution was evaporated to dryness and the residue solidified in ethyl acetate. The chloride (177) crystallised from ethanol-ethyl acetate.

To a solution of 5.0 g. of the chloride (177) in 50 ml. of 2N.HCl at 0° was added an excess of aqueous sodium nitrite. The solution was kept at 0° for 10 minutes. The resulting precipitate was filtered and dried. The crude product, (178,X=Cl), weighed 3.5 g. (67%). The perchlorate (178,X=ClO_4) was prepared by dissolving the chloride (178, X=Cl) in a solution of 65% perchloric acid and precipitated on the addition of ethanol. Crystallisation from ethanol

SYNTHESES OF 2-ALKYLQUINOLIZINIUM SALTS.

containing a few drops of 65% perchloric acid gave white crystals of m.p. 238°.

$C_{11}H_9N_3O_4ClBr$ requires: C, 36.43; H, 2.50; N, 11.59%

Found: C, 36.85; H, 2.60: N, 11.31%

Nitrosation of 1-Amino-3-methylquinolizinium Chloride, (167, X=Cl).

The chloride (167,X=Cl) was obtained by passing a solution of 1-amino-3-methylquinolizinium bromide (167,X=Br) down an ion-exchange column (Amberlite IRA 400,Cl). The solution was evaporated to dryness and the residue solidified in ethyl acetate. Crystallisation from ethanol-ethyl acetate gave the chloride (167,X=Cl).

To a solution of 2.0 g. of the chloride (167,X=Cl) in 20 ml. of 2N.HCl at room temperature was added an excess of aqueou sodium nitrite. The resulting precipitate was filtered, dried and crystallised from ethanol, giving 1.5 g. (78%) of compound (A), as yellow needles, m.p. 165°.

$C_{10}H_9N_3O$ requires: C, 64.16; H, 4.85; N, 22.45%

Found: C, 63.67; H, 4.86; N, 22.30%

Preparation of Compound (B).

A solution of compound (A) in ethanol containing a few drops of piperidine was kept at room temperature for 1 hour. The solvent was concentrated to a small volume when the compound (B) crystallised. Recrystallisation from ethanol

gave a white amorphous solid of m.p. 205°.

$C_{10}H_9N_3O$ requires: C, 64.16; H, 4.85; N, 22.45%

Found: C, 63.61; H, 4.95; N, 22.55%

1-Oxo-2-oximino-1,2,3,4-tetrahydroquinolizinium Chloride, (185, X = Cl)

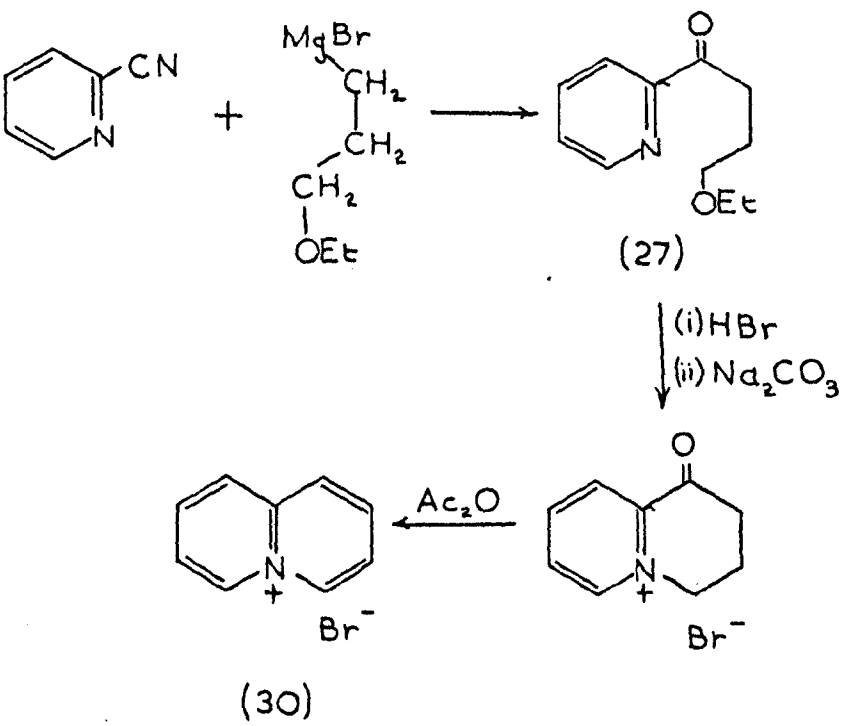
A solution of 10.0 g. of the ketone (29) and 3.0 g. of amyl nitrite in 300 ml. of ethanol was cooled to 0°. A stream of dry hydrogen chloride gas was bubbled through the solution for 3 hours. During this time a yellow solid precipitated from the solution and was filtered off. The filtrate was evaporated to dryness and the residue solidified in ethyl acetate giving a further crop of the yellow solid. The two crops were combined and dissolved in water. The aqueous solution was percolated through a chloride-exchange column (Amberlite IRA 400, Cl) and then evaporated to dryness. The residue solidified in ethyl acetate and crystallised from ethanol giving 7.7 g. (66%) of the chloride (187, X = Cl), m.p. 230°. A specimen of the chloride (187, X = Cl) was purified for analysis by Mr. P. Gay.

$C_9H_9N_2O_2Cl$ requires: C, 42.05; H, 3.53; N, 10.9%

Found: C, 41.6; H, 3.63; N, 11.5%

Discussion.

Although the literature contains numerous references to the preparation of alkylquinolizinium salts, the only reported general synthesis of 2-alkylquinolizinium compounds is that by Nesmeyanov and Rybinskaia[14]. The authors describe the preparation of 2-methyl, 2-propyl and 2-phenylquinolizinium salts by the condensation of 2-picolyl-lithium with suitable keto-acetals. The alternative syntheses are modifications of the original synthesis of quinolizinium bromide (30) by Glover and Jones[15].

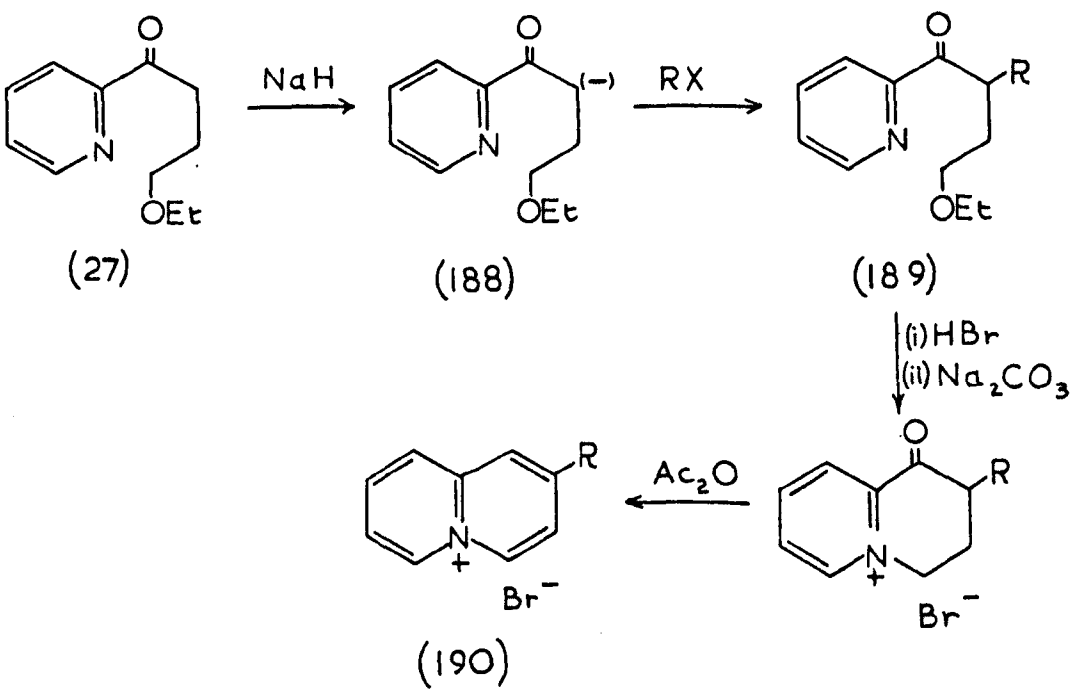


(30)

Thus, Moynehan, Schofield, Jones and Katritsky[71] have prepared 2-methylquinolizinium bromide by using 3-methyl-2-cyanopyridine

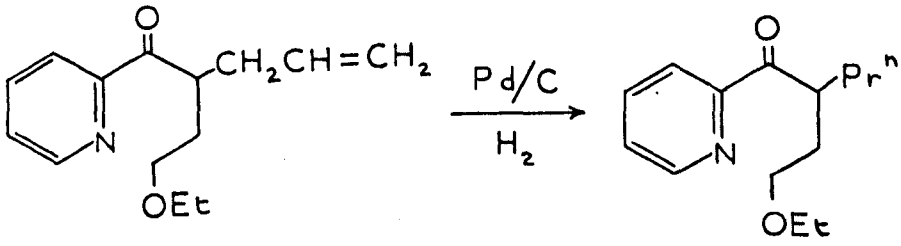
in the above reaction scheme. Glover and Jones[16] modified the alkyl precursor in the first reaction to obtain 2-alkylquinolizinium compounds by the same route. Miyadera and Iwiai[17] employed a substituted keto-lactone in a condensation reaction with ethyl picolinate, the final product being 2-methylquinolizinium bromide. An account will now be given of a further extension of this work to include a general synthesis of 2-alkylquinolizinium salts.

The ketone (27) was available in good yield by the procedure outlined above and offered a route to 2-alkylquinolizinium salts. The alkylation of the ketone (27) would proceed in the position adjacent to the carbonyl group and then the usual procedure of cyclising in hydrobromic acid and aromatising in acetic anhydride, would give 2-alkylquinolizinium salts, (190).



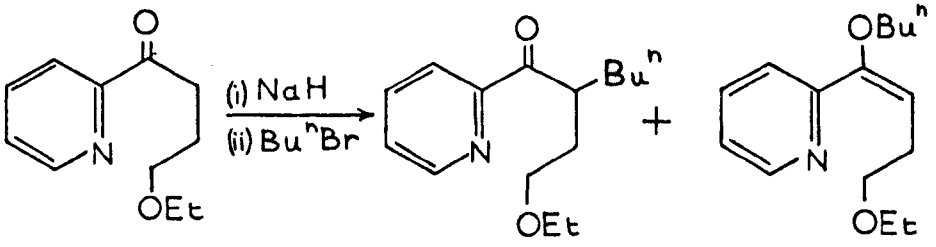
(27) (188) (189) (190)

The ketone (27) was alkylated by first preparing the enolate (188) in a refluxing solution of the ketone and sodium hydride in dimethoxy ethane. The addition of an alkyl halide RX to the cooled solution followed by a short period at the boiling point gave alkylated ketones of the type (189). By this general procedure the alkylated ketones (189, R=CH_3), (189, R=CH_2Ph) and (189, R=allyl) were obtained in 50-60% yields using methyl iodide, benzyl bromide and allyl bromide, respectively. The ketone (189, R=allyl) was reduced in 69% yield to the ketone (189, R=Pr^n).



The use of n-butyl bromide as the alkyl halide in the alkylation reaction gave a mixture of compounds. By fractional distillation of the reaction mixture it was possible to isolate two major fractions. The first consisted of the starting ketone (27). The second consisted of two components, as indicated by gas chromatography. The nuclear magnetic resonance spectrum of the mixture of two components was

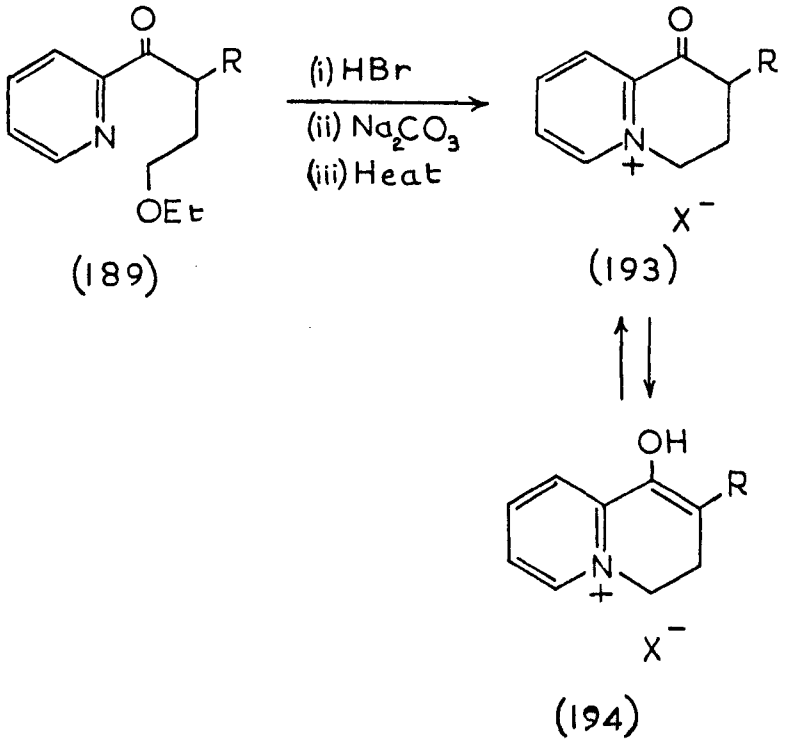
explicable in terms of an O-alkylated product (192) and the required C-alkylated product (191). The presence of the O-alkylated material was confirmed by treatment of the mixture with hot hydrochloric acid causing cleavage of the ether bond and producing the starting ketone (27). Fractional distillation of this new mixture then gave ketone (27) and the C-alkylated material (191). The overall yield of (191) was 15% (47% based on ketone used).



(27) (191) (192)

Attempts were made to improve the yield of the C-alkylated compound (191) by using n-butyl-toluene-p-sulphonate in place of n-butyl bromide. The previous experiments with the more reactive alkyl halides gave exclusively C-alkylated products and by employing a n-butyl compound with a better leaving group it was hoped to minimise the yield of the O-alkylated material (192). The reaction, performed under the same conditions, however, gave a mixture of the C- and O-alkylated compounds, in approximately the same proportions as before.

The alkylated ketones (189 ,R=CH_2Ph) and (189 ,R=Pr^n) were cyclised in the usual manner by first boiling in hydrobromic acid and then heating the chloroform extracts of the basified solution. Both of the ketones cyclised readily. The nuclear magnetic resonance and infrared spectra of the crude reaction products, however, showed that mixtures of the keto and enol tautomers (193,194, R=CH_2Ph, Pr^n, X=Br) of the cyclised materials were present.

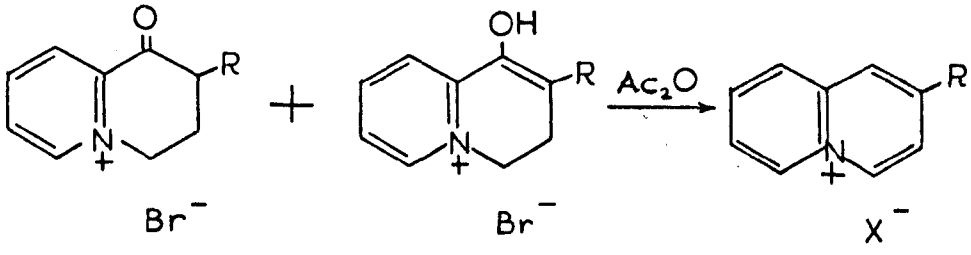


(189) (193) (194)

The mixture of benzyl tautomers (193 , 194,R=CH_2Ph,X=Br) showed absorption at 1700 $cm.^{-1}$ in the infrared spectrum. When the mixture was recrystallised, however, the enol form (194, R=CH_2Ph,X=Br) was obtained exclusively, showing no absorption

above 1660 cm.$^{-1}$. The mixture of propyl tautomers (193,194, R=Pr^{n},X=Br) recrystallised to give exclusively the keto form (193,R=Pr^{n},X=Br), showing absorption at 1725 cm.$^{-1}$. The enol was obtained as the picrate (194,R=Pr^{n},X=picrate) from the keto-bromide (193,R=Pr^{n},X=Br).

The enol (194,R=CH_2Ph,X=Br) aromatised in refluxing acetic anhydride to the 2-benzylquinolizinium salt (190,R=CH_2Ph). The keto-enol mixture (193,194,R=Pr^{n},X=Br) aromatised under the same conditions to 2-n-propylquinolizinium salt (190,R=Pr^{n}).



(193) (194) (190)

The value of these reactions as a general synthesis of 2-alkylquinolizinium salts depends upon the success of the initial alkylation reaction. The results suggest that less reactive alkyl halides, such as n-butyl bromide, are unsuitable for use in this reaction. However, by employing allylic halides, such as allyl bromide, the alkylation would proceed in good yield and by reduction of the allylic double-bond it would be possible to obtain a number of simple substituted ketones of the type (189) and, subsequently, the corresponding 2-alkylquinolizinium salts.

Experimental.

Syntheses of the Ketones (189, R=Me, CH_2Ph, allyl, Pr^n).

A stirred solution of 5.7 g. (0.03 moles) of the ketone (27) and 1.5 g. of sodium hydride (50% dispersion in liquid paraffin) in 100 ml. of dry dimethoxy ethane was boiled under reflux for 1 hour. To the cooled solution at 0° was added 0.03 moles of the alkyl halide. The mixture was then boiled for 1 hour, during which time sodium halide was precipitated. The solvent was removed and the residue treated with 5N-hydrochloric acid and ether. The acid layer was separated and basified with ammonia (d.0.88). The alkylated ketone (189) was extracted with ether and the dried ethereal solution distilled.

(a) 2-(4-Ethoxy-2-methylbutanoyl)pyridine, (189, R=CH_3), was obtained in 52% yield using methyl iodide in the above alkylation reaction and had b.p. $144-147^\circ/15$ mm. The infrared spectrum of this compound was identical to that of a specimen prepared by Glover and Jones[15].

(b) 2-(2-Benzyl-4-ethoxybutanoyl)pyridine, (189, R=CH_2Ph), was obtained in 66% yield using benzyl bromide and had b.p. $138-141^\circ/0.02$ mm.

$C_{18}H_{21}NO_2$ requires; C, 76.3; H, 7.45; N, 4.95%

Found: C, 76.3; H, 7.35; N, 5.3%

$\nu_{max.}(CCl_4)$ 1695, 1130, 1115 $cm.^{-1}$

(c) 2-(2-Allyl-4-ethoxybutanoyl)pyridine, (189, R=allyl), was obtained in 61% yield using allyl bromide and had b.p. 95-98°/0.06 mm.

$C_{14}H_{19}NO_2$ requires: C, 72.05; H, 8.2; N, 6.0%

Found: C, 72.0; H, 7.9; N, 5.6%

$\nu_{max.}$(film) 1695,1645,1120,920 $cm.^{-1}$

(d) 2-(4-ethoxy-2-n-propylbutanoyl)pyridine, (189, R=Pr^n), was obtained by the reduction of the allyl-ketone (189,R=allyl). A solution of 1.6 g. of the ketone (189,R=allyl) in 30 ml. of 95% ethanol with 0.2 g. of 10% palladium charcoal was stirred under hydrogen at atmospheric temperature and pressure. After the uptake of 1.1 moles of hydrogen the solution was filtered and evaporated under reduced pressure. The product distilled at 122-124°/0.5 mm. in 1.1 g. (69%) yield.

$C_{14}H_{21}NO_2$ requires: C, 71.45; H, 9.00; N, 5.95%

Found: C, 71.3; H, 8.75; N, 5.9%

$\nu_{max.}$(film) 1690,1110 $cm.^{-1}$, no absorption at 1645 or 920 cm^{-1}.

(e) 2-(2-n-Butyl-4-ethoxybutanoyl)pyridine, (191), was obtained as one of a mixture of three components from the alkylation of 11.6 g. of the ketone (27) with 0.06 moles of n-butyl bromide. Distillation of the reaction mixture gave a first fraction of b.p. 105-109°/0.25 mm., weighing

3.1 g. A second fraction had b.p. 109-130°/0.25 mm. and weighed 8.0 g. The first fraction consisted almost entirely of the starting ketone (27). The second fraction consisted of the starting ketone (27), the O-alkylated compound (192) and the C-alkylated material (191). An estimate from the g.l.c. peaks led to yields of 52% of recovered ketone (27), 15% of (191) and 8% of (192). The second fraction was redistilled and later fractions weighing 4.3 g. were heated with 5N-hydrochloric acid for 30 minutes at 100°. The acid solution was treated with ether and the ethereal solution separated, dried and distilled. The residue was fractionally distilled giving a forerun of b.p. 80-86°/0.03 mm., weighing 3.0 g., and the C-alkylated product (191) of b.p. 92-93°/0.03 mm., weighing 0.4 g.

$C_{15}H_{23}NO_2$ requires: C, 72.25; H, 9.3%

Found; C, 71.9; H, 9.0%

$\nu_{max.}$ (film) 1695 $cm.^{-1}$

Cyclisation of the Ketones (189, R=CH_2Ph) and (189, R=Pr^n).

Solutions of the ketones in 48% hydrobromic acid were boiled under reflux for 1 hour. The acid was removed under reduced pressure and each residue dissolved in water. The cyclised ketones were obtained by extraction from the aqueous solution with chloroform during the dropwise

addition of aqueous sodium carbonate. The chloroform solution was dried (sodium sulphate) and boiled for 1 hour. The chloroform was then distilled and each residue solidified on addition of ethyl acetate.

(a) 2-Benzyl-3,4-dihydro-1-hydroxyquinolizinium bromide, (194, R=CH_2Ph, X=Br), was obtained by crystallisation of the solid residue from ethanol-ethyl acetate, m.p. 160-161.5°.

$C_{16}H_{16}NOBr$ requires: C, 60.4; H, 5.07; N, 4.4%

Found: C, 60.7; H, 4.65; N, 4.4%

$\lambda_{max.}$ (H_2O) 2440, 2680, 3380 Å. (log. 3.80, 3.87, 3.80)

(b) 3,4-Dihydro-1-hydroxy-2-n-propylquinolizinium picrate, (194, R=Pr^n, X=picrate), was obtained as follows. The solid residue from the cyclisation reaction crystallised from ethanol-ethyl acetate giving the keto-bromide (193, R=Pr^n, X=Br), $\nu_{max.}$ 1725 $cm.^{-1}$. An aqueous solution of this ketone was added to aqueous sodium picrate. The resulting precipitate was the enol-picrate (194, R=Pr^n, X=picrate) and crystallised from ethanol, m.p. 147-149°.

$C_{18}H_{18}N_4O_8$ requires: C, 51.67; H, 4.34; N, 13.4%

Found: C, 51.5; H, 4.15; N, 12.7%

2-Benzylquinolizinium Picrate, (190, R=CH_2Ph, X=picrate).

A solution of the enol (194, R=CH_2Ph, X=Br) in acetic anhydride was boiled under reflux for 1 hour. The solution

was evaporated to dryness under reduced pressure. The residue was dissolved in water and added to aqueous sodium picrate. The resulting picrate (190, R=CH_2Ph, X=picrate) crystallised from ethanol as yellow needles, m.p. 160-162°.

$C_{22}H_{16}N_4O_7$ requires: C, 58.95; H, 3.6; N, 12.5%

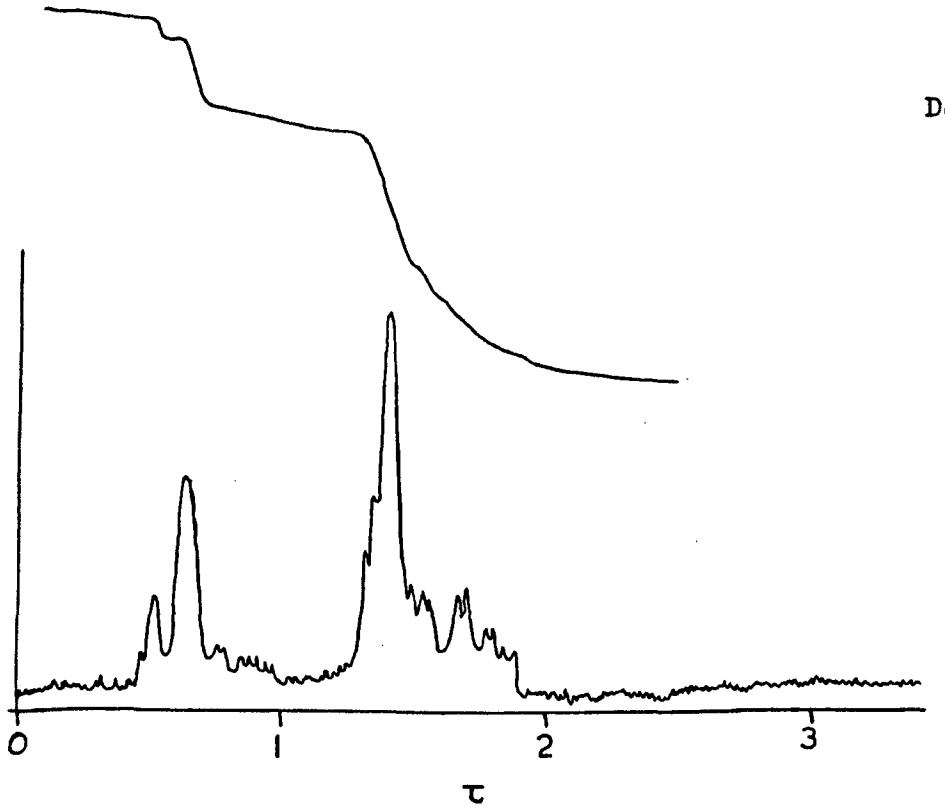
Found: C, 59.0; H, 3.3; N, 12.1%

2-n-Propylquinolizinium Bromide, (190, R=Pr^n, X=Br).

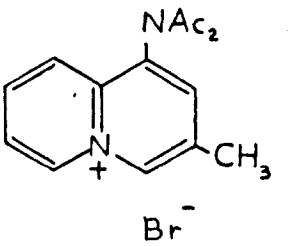
The keto-enol mixture (193, 194, R=Pr^n, X=Br), was obtained as the solid residue from the cyclisation reaction and aromatised by the preceding method. The residue from the reaction solidified in ethyl acetate and crystallised from ethanol-ethyl acetate giving the quinolizinium salt (190, R=Pr^n, X=Br), m.p. 129-132°, (lit.[14] 133-135°).

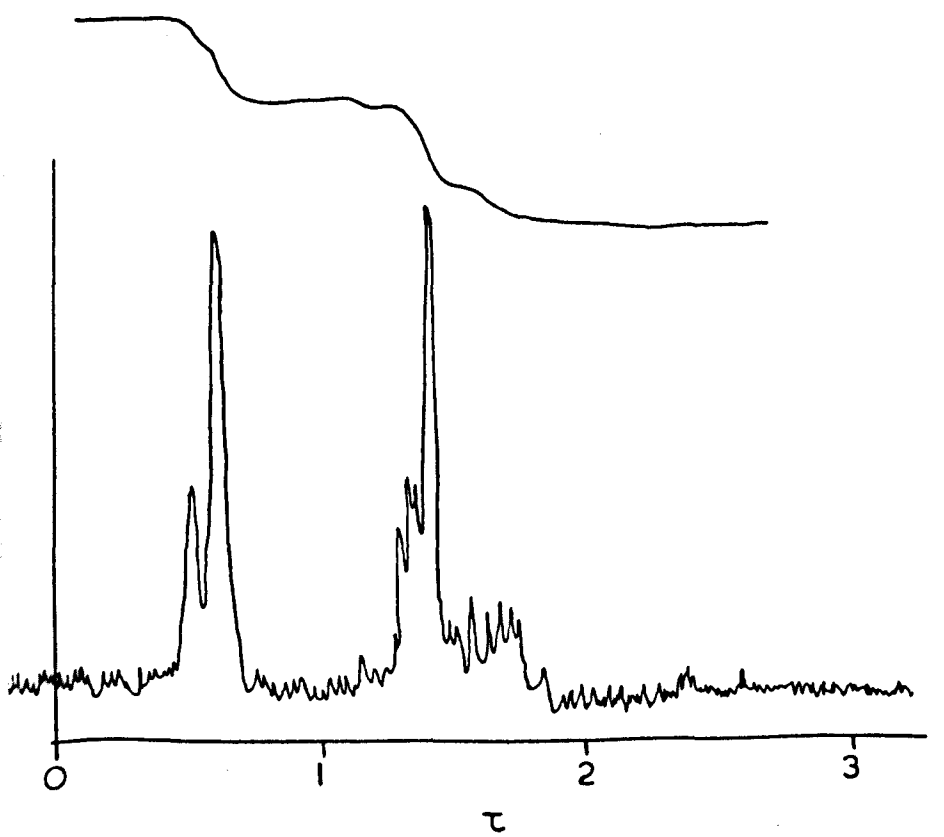
$\lambda_{max.}$ (H_2O) 3120, 3190, 3260 Å.

NUCLEAR MAGNETIC RESONANCE SPECTRA



Solvent:
Deuterium Oxide





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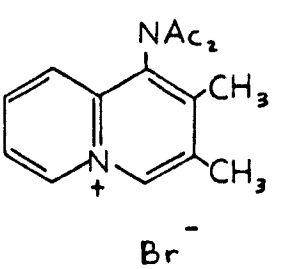

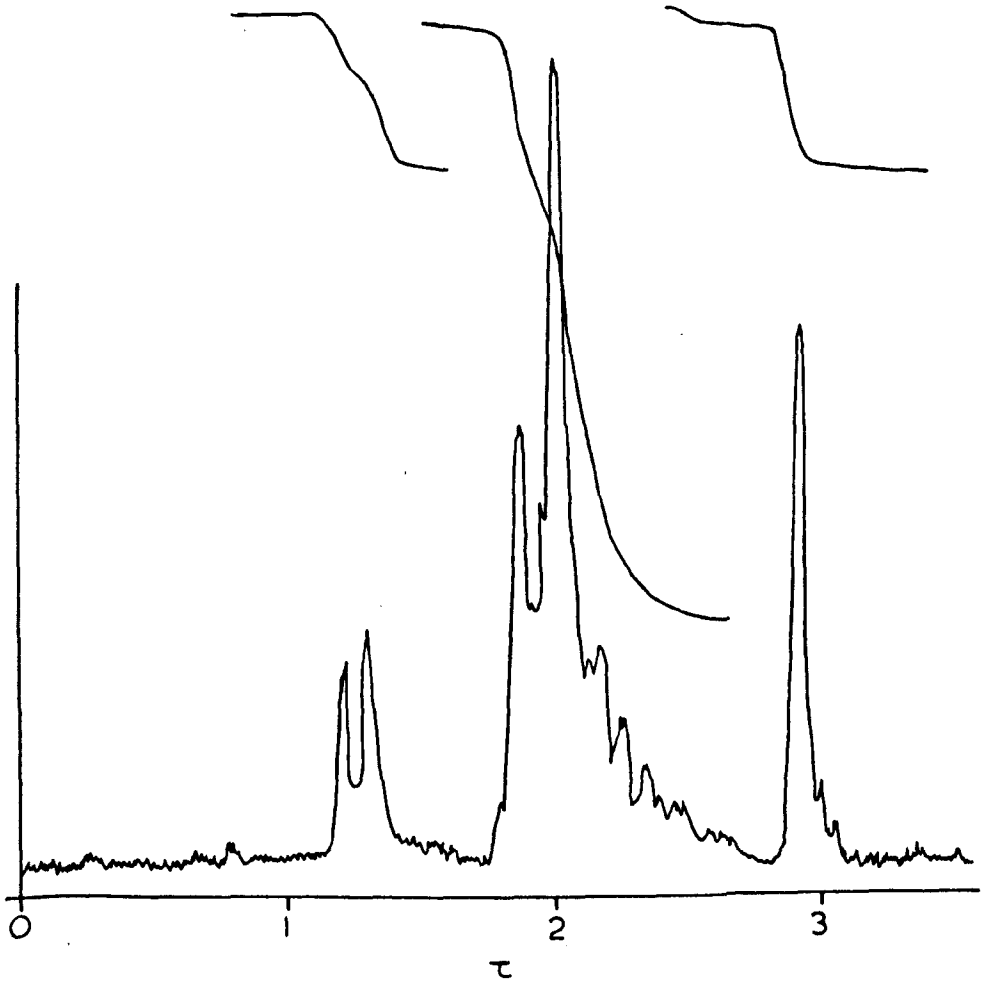

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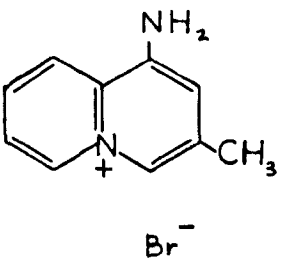

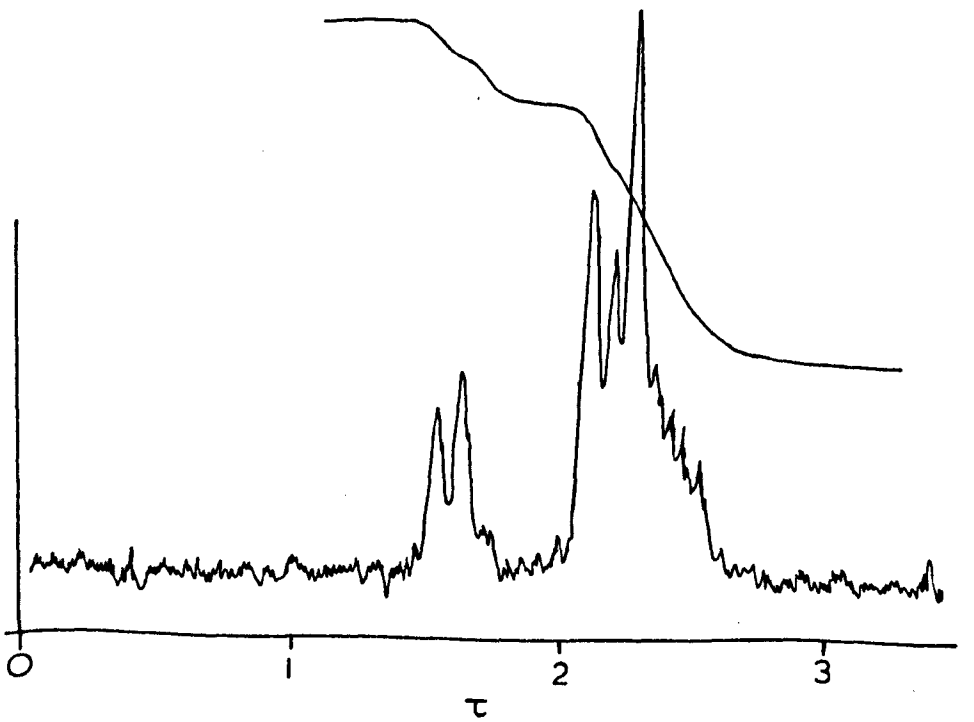

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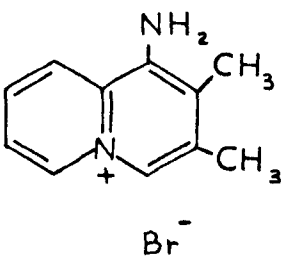
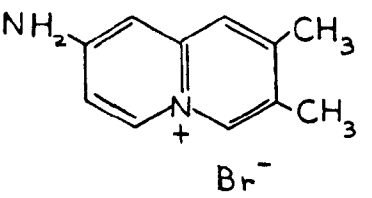
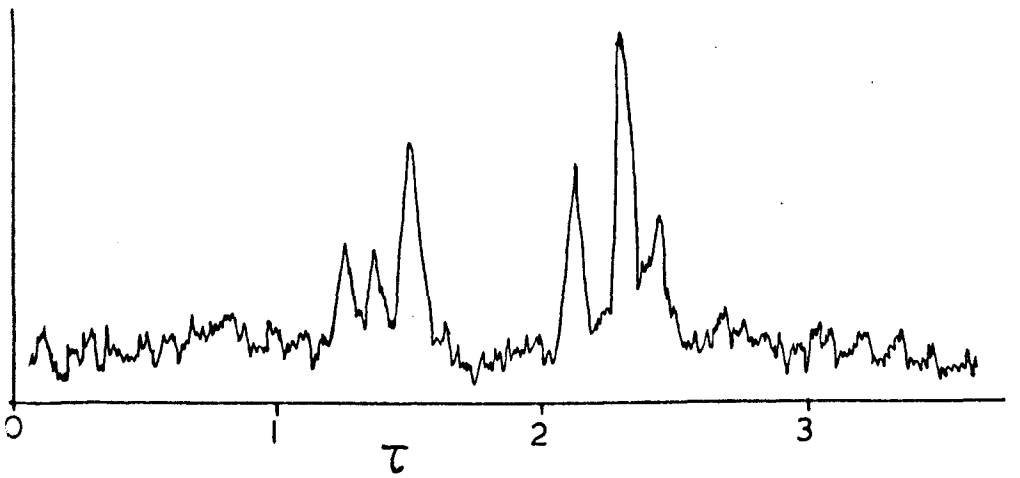


Solvent:

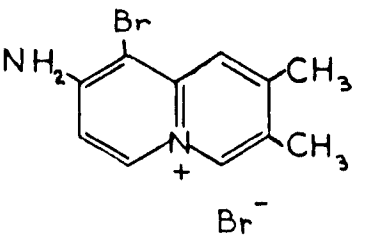
Trifluoracetic Acid

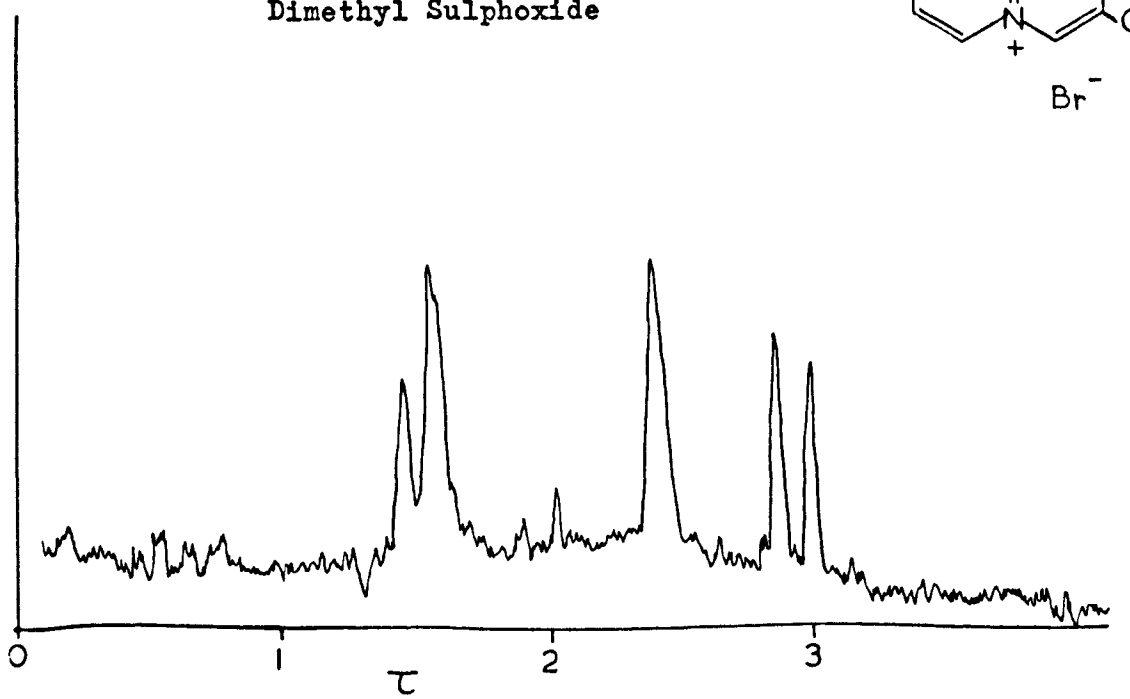


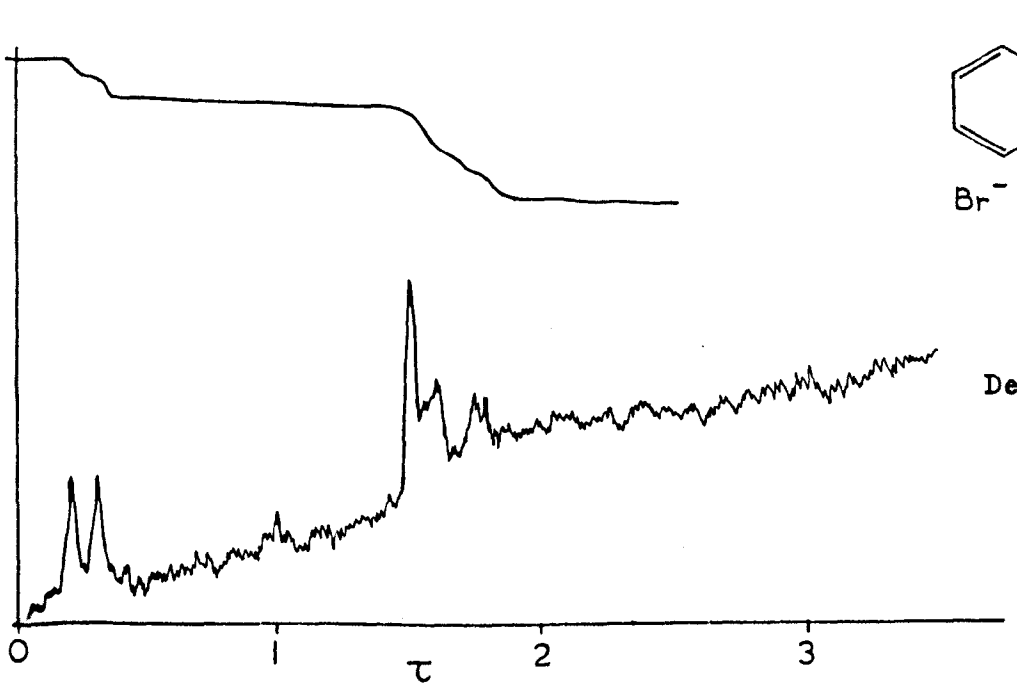


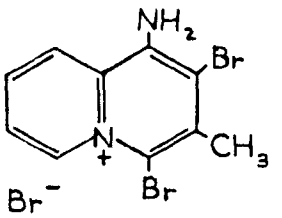
Solvent:

Dimethyl Sulphoxide









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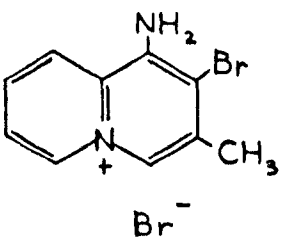

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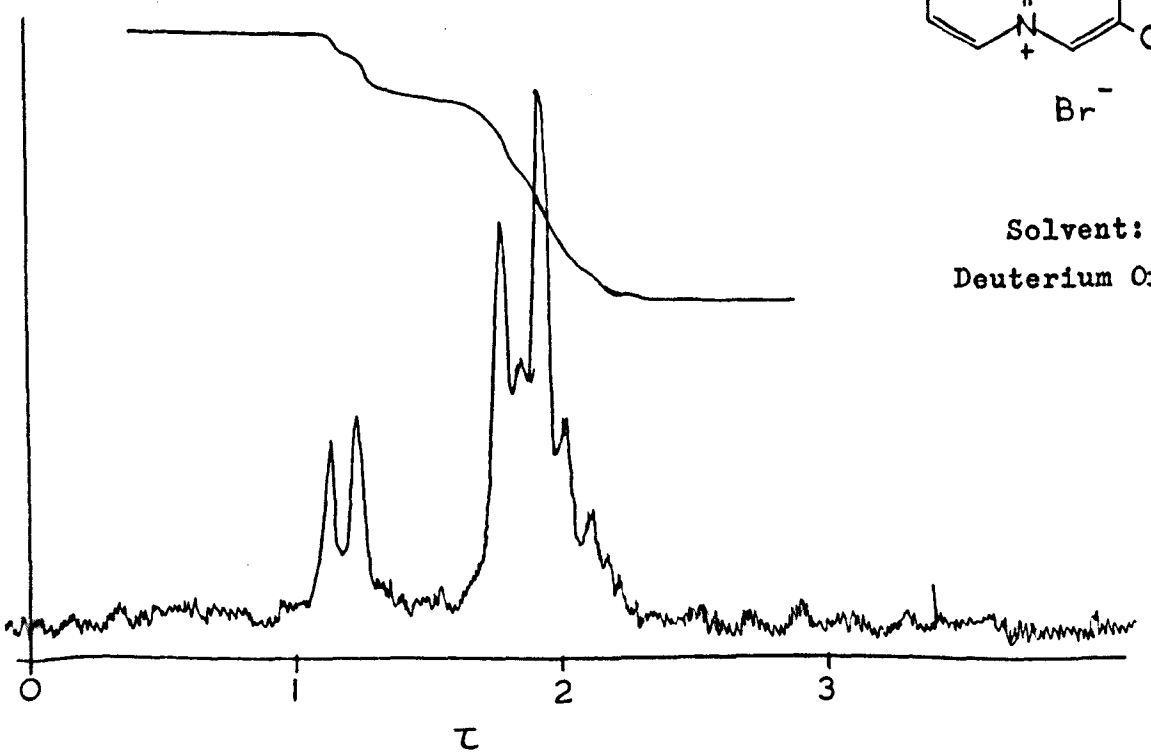

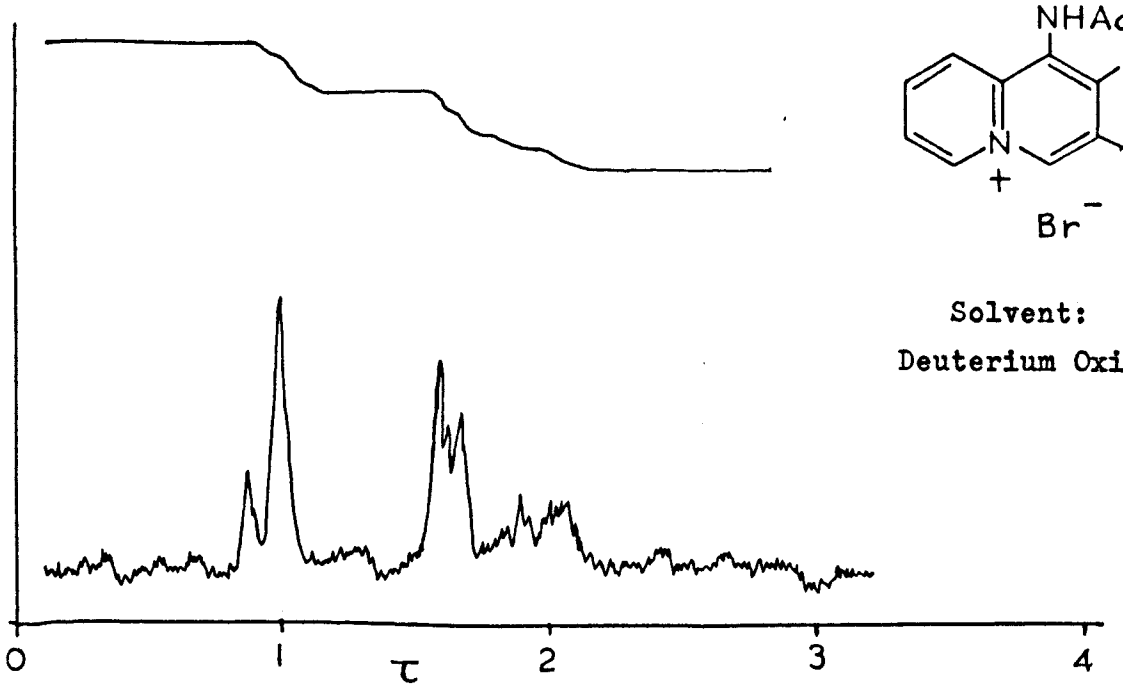

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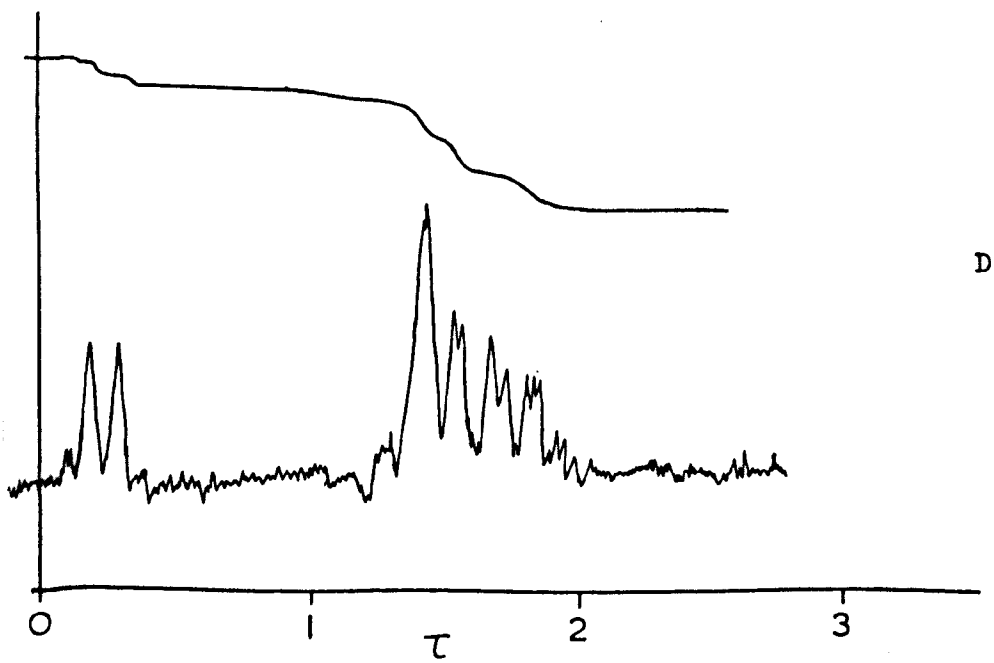

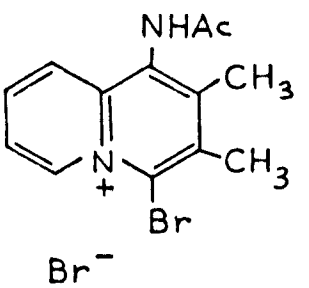

Solvent:
Deuterium Oxide

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